<table>
<thead>
<tr>
<th>Project Title</th>
<th>Supervisor First and Last Name</th>
<th>Department</th>
<th>Contact Person First and Last Name</th>
<th>Telephone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensuring patient don’t just survive but thrive after cardiac surgery.</td>
<td>Rakesh Arora</td>
<td>Internal Medicine</td>
<td>Rakesh Arora</td>
<td>258-1078</td>
<td><a href="mailto:rarora@sbggh.mb.ca">rarora@sbggh.mb.ca</a></td>
</tr>
<tr>
<td>Developmental Origins of Health and Disease in The Manitoba Personalized Lifestyle Study</td>
<td>Meghan Azad</td>
<td>Pediatrics and Child Health</td>
<td>Meghan Azad</td>
<td>204-975-7754</td>
<td><a href="mailto:meghan.azad@umanitoba.ca">meghan.azad@umanitoba.ca</a></td>
</tr>
<tr>
<td>A descriptive study evaluating the clinical use of Olinobuzumad (GAZYYA+ including demographics, indications, CIRS, cytogenetics and prognostic markers, toxicities, adherence and financial impact and duration of treatment for front line therapy for chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) compared to other front line therapies</td>
<td>Versha Banerji</td>
<td>Internal Medicine</td>
<td>Versha Banerji</td>
<td>204-787-1884</td>
<td><a href="mailto:vbanerji1@cancercare.mb.ca">vbanerji1@cancercare.mb.ca</a></td>
</tr>
<tr>
<td>Rapid detection of antimicrobial resistant Enterobacterial outer membrane vesicles</td>
<td>Denice Bay</td>
<td>Medical Microbiology &amp; Infectious Diseases</td>
<td>Denice Bay</td>
<td>2048949160</td>
<td><a href="mailto:Denice.Bay@umanitoba.ca">Denice.Bay@umanitoba.ca</a></td>
</tr>
<tr>
<td>Elucidating the mechanism of action of a novel molecule with antibacterial activity</td>
<td>Silvia Cardona</td>
<td>Medical Microbiology &amp; Infectious Disease</td>
<td>Silvia Cardona</td>
<td>204-474-8997</td>
<td><a href="mailto:silvia.cardona@umanitoba.ca">silvia.cardona@umanitoba.ca</a></td>
</tr>
<tr>
<td>Zika virus-induced proteomic effects in 3-D cell culture</td>
<td>Kevin Coombs</td>
<td>Medical Microbiology</td>
<td>Kevin Coombs</td>
<td>204-789-3976</td>
<td><a href="mailto:kevin.coombs@umanitoba.ca">kevin.coombs@umanitoba.ca</a></td>
</tr>
<tr>
<td>The impact of frailty on clinical outcomes for stage IV non-small cell lung cancer patients receiving chemotherapy</td>
<td>David Dawe</td>
<td>Internal Medicine</td>
<td>David Dawe</td>
<td>204-396-7936</td>
<td><a href="mailto:didawe@cancercare.mb.ca">didawe@cancercare.mb.ca</a></td>
</tr>
<tr>
<td>Developing algorithms to accurately and efficiently identify breast and colorectal cancer recurrence</td>
<td>Kathleen Decker</td>
<td>Community Health Sciences</td>
<td>Kathleen Decker</td>
<td>204-787-1567</td>
<td><a href="mailto:kdecker@cancercare.mb.ca">kdecker@cancercare.mb.ca</a></td>
</tr>
<tr>
<td>Neoadjuvant F4A-D4 Chemotherapy in Invasive Breast Cancer: The Manitoba Experience</td>
<td>Danielle Desaulles</td>
<td>Internal Medicine</td>
<td>Danielle Desaulles</td>
<td>204-787-1815</td>
<td><a href="mailto:ddesaulles@cancercare.mb.ca">ddesaulles@cancercare.mb.ca</a></td>
</tr>
<tr>
<td>Strategies to enhance benefits of allogeneic stem cell therapy for cardiac regeneration.</td>
<td>Sanjiv Dhirga</td>
<td>Physiology</td>
<td>Sanjiv Dhirga</td>
<td>204-235-3454</td>
<td><a href="mailto:sdhirga@srb.ca">sdhirga@srb.ca</a></td>
</tr>
<tr>
<td>Diabetes, metformin, and the development of rheumatoid arthritis</td>
<td>Hani El-Gabalawy</td>
<td>Internal Medicine</td>
<td>Hani El-Gabalawy</td>
<td>204-787-2208</td>
<td><a href="mailto:hani.elgalawy@umanitoba.ca">hani.elgalawy@umanitoba.ca</a></td>
</tr>
<tr>
<td>Impact of adjuvant chemotherapy initiation, completion and discontinuation on recurrence and survival rates in patients with colon cancer</td>
<td>Tunji Fatoye</td>
<td>Family Medicine</td>
<td>Tunji Fatoye</td>
<td>204-632-3203</td>
<td><a href="mailto:tfatoye@sogh.mb.ca">tfatoye@sogh.mb.ca</a></td>
</tr>
<tr>
<td>The impact of LAG3 on lymphocyte susceptibility to HIV infection</td>
<td>Keith Fowke</td>
<td>Medical Microbiology &amp; Infectious Disease</td>
<td>Keith Fowke</td>
<td>204-789-3818</td>
<td><a href="mailto:keith.fowke@umanitoba.ca">keith.fowke@umanitoba.ca</a></td>
</tr>
<tr>
<td>Real-world experience with procarbazine, CCNU and vincristine (PCV) chemotherapy after radiotherapy (RT) for grade II and III gliomas</td>
<td>Craig Harlos</td>
<td>Medical Oncology and Hematology</td>
<td>Craig Harlos</td>
<td>2047872128</td>
<td><a href="mailto:charlos@cancercare.mb.ca">charlos@cancercare.mb.ca</a></td>
</tr>
<tr>
<td>Explore the effects of diet and genetics on inflammatory bowel disease pathogenesis</td>
<td>Pingzhao Hu</td>
<td>Biochemistry and Medical Genetics</td>
<td>Pingzhao Hu</td>
<td>204-789-3229</td>
<td><a href="mailto:pingzhao.hu@umanitoba.ca">pingzhao.hu@umanitoba.ca</a></td>
</tr>
<tr>
<td>Flaxseed in the mitigation against anthracycline and trastuzumab mediated cardiotoxicity (FANTAM study)</td>
<td>Davinder Jassal</td>
<td>Internal Medicine</td>
<td>Davinder Jassal</td>
<td>237-2023</td>
<td><a href="mailto:djassal@sbggh.mb.ca">djassal@sbggh.mb.ca</a></td>
</tr>
<tr>
<td>Investigating the Neuroprotective Role of Neuregulin-1 in Traumatic Spinal Cord Injury</td>
<td>Soheila Karimi</td>
<td>Physiology and Pathophysiology</td>
<td>Soheila Karimi</td>
<td>204-272-3109</td>
<td><a href="mailto:soheila.Karimi@umanitoba.ca">soheila.Karimi@umanitoba.ca</a></td>
</tr>
<tr>
<td>Development and evaluation of new therapeutic targets for multiple sclerosis</td>
<td>Soheila Karimi</td>
<td>Physiology and Pathophysiology</td>
<td>Soheila Karimi</td>
<td>204-272-3109</td>
<td><a href="mailto:soheila.Karimi@umanitoba.ca">soheila.Karimi@umanitoba.ca</a></td>
</tr>
<tr>
<td>Towards a prenatal therapy for abnormal lung development and congenital diaphragmatic hernia; using non-coding RNAs to improve lung development before these babies are even born.</td>
<td>Richard Keijzer</td>
<td>Surgery</td>
<td>Richard Keijzer</td>
<td>2049757781</td>
<td><a href="mailto:Richard.keijzer@umanitoba.ca">Richard.keijzer@umanitoba.ca</a></td>
</tr>
<tr>
<td>A tale of Legionella and HIV dual infection: understanding lung inflammation, lung damage and disease</td>
<td>Yoav Keynan</td>
<td>Internal Medicine</td>
<td>Yoav Keynan</td>
<td>204-977581</td>
<td><a href="mailto:yoav.keynan@umanitoba.ca">yoav.keynan@umanitoba.ca</a></td>
</tr>
<tr>
<td>Characterization of influenza-bacterial co-infection molecular pathogenesis in a co-culture model of the alveolar-capillary barrier</td>
<td>Jason Kindrachuk</td>
<td>Medical Microbiology &amp; Infectious Diseases</td>
<td>Jason Kindrachuk</td>
<td>2047893807</td>
<td><a href="mailto:jason.kindrachuk@umanitoba.ca">jason.kindrachuk@umanitoba.ca</a></td>
</tr>
<tr>
<td>Selective knockdown of misfolded SOD1 as a therapy for amyotrophic lateral sclerosis</td>
<td>Jiming Kong</td>
<td>Human Anatomy and Cell Science</td>
<td>Jiming Kong</td>
<td>2049775601</td>
<td><a href="mailto:Jiming.Kong@umanitoba.ca">Jiming.Kong@umanitoba.ca</a></td>
</tr>
<tr>
<td>Title: Analysis of Corynabacterium diphtheriae using Whole Genome Sequencing (WGS) as a molecular typing tool , with a focus on strains circulating in Manitoba</td>
<td>Philippe Lagace-Wiens</td>
<td>Medical Microbiology</td>
<td>Kathy Bernard</td>
<td>1-204-789-2135</td>
<td><a href="mailto:kathy.bernard@phac-aspc.gc.ca">kathy.bernard@phac-aspc.gc.ca</a></td>
</tr>
<tr>
<td>Congenital surgical anomalies long-term follow up study – link with Manitoba Centre for Health Policy</td>
<td>Suayan Lum Min</td>
<td>Surgery</td>
<td>Suayan Lum Min</td>
<td>204-787-4203</td>
<td><a href="mailto:slummin@exchange.hsc.mb.ca">slummin@exchange.hsc.mb.ca</a></td>
</tr>
<tr>
<td>Magnitude and spectrum of antibodies targeting HIV protease cleavage sites and their correlation with resistance to HIV-1 infection in the Pumwani Sex Worker cohort</td>
<td>Ma Luo</td>
<td>Medical Microbiology</td>
<td>Ma Luo</td>
<td>204-789-5072</td>
<td><a href="mailto:Ma.Luo@umanitoba.ca">Ma.Luo@umanitoba.ca</a></td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
<td>Affiliations</td>
<td>Phone</td>
<td>Email</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>---------------------------------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Nuclear remodeling of the genome in cancer cells</td>
<td>Sabine Mai</td>
<td>Physiology and Pathophysiology</td>
<td>2047872135</td>
<td><a href="mailto:sabine.mai@umanitoba.ca">sabine.mai@umanitoba.ca</a></td>
<td></td>
</tr>
<tr>
<td>Resolving the immunological abnormalities in chronic lymphocytic leukemia and their relevance to patient outcomes</td>
<td>Aaron Marshall</td>
<td>Immunology</td>
<td>204 789-3385</td>
<td><a href="mailto:aaron.marshall@umanitoba.ca">aaron.marshall@umanitoba.ca</a></td>
<td></td>
</tr>
<tr>
<td>Does SYTNAX score predict outcomes in Cardiogenic Shock ?</td>
<td>Kunal Minhas</td>
<td>Internal Medicine - Cardiology</td>
<td>204-237-2390</td>
<td><a href="mailto:kminhas@sbgh.mb.ca">kminhas@sbgh.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>Lipid molecules as a predictive factor of treatment response to repetitive transcranial magnetic stimulation in major depressive disorder</td>
<td>Mandana Modirrousta</td>
<td>Medicine</td>
<td>204-237-2917</td>
<td><a href="mailto:modirrousta@sbgh.mb.ca">modirrousta@sbgh.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>Changing Trends in Presentation and Outcome of Squamous Cell Carcinoma of the Cervical Lymph Nodes of Unknown Origin</td>
<td>K.Alok Pathak</td>
<td>Surgery</td>
<td>204-7871340</td>
<td><a href="mailto:apathak@cancercare.mb.ca">apathak@cancercare.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>Standardization of Moderator Training for an Online Tool to Address Parental Vaccine Hesitancy</td>
<td>Jen Potter</td>
<td>Family Medicine</td>
<td>204 632 3203</td>
<td><a href="mailto:jpotter@sogh.mb.ca">jpotter@sogh.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>FDA-approved Drugs for Epigenetic Studies in Neural Stem Cells</td>
<td>Mojgan Rastegar</td>
<td>Biochemistry and Medical Genetics</td>
<td>204-272-3108</td>
<td><a href="mailto:mojgan.rastegar@umanitoba.ca">mojgan.rastegar@umanitoba.ca</a></td>
<td></td>
</tr>
<tr>
<td>Targeting Cell Signaling by FDA-Approved Drugs in Medulloblastoma Brain Tumor</td>
<td>Mojgan Rastegar</td>
<td>Biochemistry &amp; Medical Genetics</td>
<td>204-272-3108</td>
<td><a href="mailto:mojgan.rastegar@umanitoba.ca">mojgan.rastegar@umanitoba.ca</a></td>
<td></td>
</tr>
<tr>
<td>The effect of barium contrast on grid use in pediatric fluoroscopy</td>
<td>Martin Reed</td>
<td>Radiology</td>
<td>204-7872856</td>
<td><a href="mailto:irtlbakri@cancercare.mb.ca">irtlbakri@cancercare.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>Use of Wearable Technology in Real World Clinical Settings to Improve Patient Outcomes</td>
<td>Claudio Rigatto</td>
<td>Internal Medicine - Pediatrics and Child Health/ Children’s Hospital</td>
<td>204-632-3383</td>
<td><a href="mailto:mdinella@sogh.mb.ca">mdinella@sogh.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>The epidemiology and multi-disciplinary management of work-related concussion – how can we meet the needs of Manitoba’s workers?</td>
<td>Kelly Russell</td>
<td></td>
<td>204-480-1312</td>
<td><a href="mailto:krussell@chirm.ca">krussell@chirm.ca</a></td>
<td></td>
</tr>
<tr>
<td>A Tool to Predict Cesarean Delivery in Rural First Nations Populations</td>
<td>Alexander Singer</td>
<td>Family Medicine</td>
<td>(204) 422-8811</td>
<td><a href="mailto:kdahe075@icloud.com">kdahe075@icloud.com</a></td>
<td></td>
</tr>
<tr>
<td>Split-dose Bowel Preparation for morning Colonoscopy? A Pragmatic Randomized Controlled Trial</td>
<td>Harminder Singh</td>
<td>Internal Medicine</td>
<td>204-480-1311</td>
<td><a href="mailto:harminder.singh@umanitoba.ca">harminder.singh@umanitoba.ca</a></td>
<td></td>
</tr>
<tr>
<td>Frailty affects treatment decisions and outcomes for patients with chronic kidney disease</td>
<td>Navdeep Tangri</td>
<td>Internal Medicine - Nephrology</td>
<td>204-632-3383</td>
<td><a href="mailto:mdinella@sogh.mb.ca">mdinella@sogh.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>Oxidative analysis of modern polyethylene in total hip replacement</td>
<td>Thomas Turgeon</td>
<td>Surgery</td>
<td>204-926-1235</td>
<td><a href="mailto:tgascoyne@orthoinn.com">tgascoyne@orthoinn.com</a></td>
<td></td>
</tr>
<tr>
<td>Community member perspectives on models of care in remote isolated northern Manitoba First Nation communities</td>
<td>Ian Whetter</td>
<td>Family Medicine</td>
<td>204-795-2735</td>
<td><a href="mailto:ian.whetter@umanitoba.ca">ian.whetter@umanitoba.ca</a></td>
<td></td>
</tr>
<tr>
<td>Investigating the anti-inflammatory and cardio-protective effects of novel bioactive lipids derived from omega-3 fatty acids</td>
<td>Peter Zahradka</td>
<td>Physiology and Pathophysiology</td>
<td>204-235-3507</td>
<td><a href="mailto:peterz@sbrc.ca">peterz@sbrc.ca</a></td>
<td></td>
</tr>
<tr>
<td>Evolution and Characterization of Multi-Drug Resistant (MDR) Streptococcus pneumoniae Causing Invasive infections in Canada:SAVE 2013-2018</td>
<td>George Zhanel</td>
<td>Medical Microbiology/ Infectious Diseases</td>
<td>204 787-4902</td>
<td><a href="mailto:gzhanel@pcs.mb.ca">gzhanel@pcs.mb.ca</a></td>
<td></td>
</tr>
<tr>
<td>Investigation of Diabetes mellitus type 2 effect on neuronal cell in an in vitro model of CNS diabetic encephalopathy</td>
<td>Eftekhar Eftekharpour</td>
<td>Physiology &amp; Pathophysiology</td>
<td>204.789.3214</td>
<td><a href="mailto:eftekhar@umanitoba.ca">eftekhar@umanitoba.ca</a></td>
<td></td>
</tr>
<tr>
<td>Laparotomy or peritoneal drainage for the management of surgical necrotizing enterocolitis and spontaneous intestinal perforation</td>
<td>Anna Shawyer - Surgery</td>
<td></td>
<td></td>
<td>contact Salimi Mukhi 787-4203 or <a href="mailto:smukhi@exchange.hsc.mb.ca">smukhi@exchange.hsc.mb.ca</a> or <a href="mailto:slumming@exchange.hsc.mb.ca">slumming@exchange.hsc.mb.ca</a></td>
<td></td>
</tr>
</tbody>
</table>
Ensuring patient don’t just survive but thrive after cardiac surgery.

Overarching Goal: With this project, you will work with an interdisciplinary team to determine new ways to ensure patients don’t just survive but thrive after cardiac surgery. We will embark in a highly novel collaboration with our Lean Transformation office to combine the best of the medicine and business worlds to provide real and direct benefit to cardiac surgery patients in Manitoba.

Background: Approximately ~10% of patients require prolonged intensive care unit length of stay (prICULOS) after their cardiac operation. We have learned through our previous research, including past BSc Med Projects, that many recovering prICULOS patients have persistent chronic pain syndromes, increased frailty, new cognitive and mental health difficulties, ongoing renal issues and decreased quality of life not currently served by our discharge processes. Additionally, re-hospitalization and a lack of physician visits within 30 days from hospital discharge pose a significant risk factor for poor 1-year non-institutional survival for these patients. Previous Work: Our past BSc Med student has undertaken important focus group analyses to determine: 1. patient-centered values and difficulties following discharge from hospital after cardiac surgery; 2. potential barriers to successful discharge from hospital; 3. caregiver-centered values and difficulties during hospital discharge and in the community; 4. cardiac surgeon’s perspectives on patient-centered and caregiver-centered values and difficulties following discharge from hospital after cardiac surgery. We will now seek to implement improvements in the themes identified to determine efficacy in reducing rehospitalization and improving health related quality of life (HRQoL) in vulnerable older adult cardiac surgery patients. Working Hypothesis: Development of new discharge planning processes with improvements in patient-caregiver perceptions of their health will result in enhanced functional recovery and improved quality of life at 1-year following hospital discharge after their cardiac surgery procedure. Study Design: The proposed study is a single centre, prospective, mixed methods cohort study that will be undertaken at the St. Boniface Hospital. This will involve designing surveys and holding focus group sessions with key stakeholders involved in the care of patient’s operative and recovery periods. In addition, we will work with a large interdisciplinary team and Lean Transformation to develop and implement a new discharge/transition process to meet the needs of the vulnerable older adult patient. Feasibility: We have established a network of community care providers and in alignment with the WRHA priority of “building sustainability” with the development of a new transition process and improving access to appropriate person-centered preventive and rehabilitative care in the Manitoba healthcare system. Student’s Role: The student will be an integral member of the team and will work on ethics submission, study design and execution, manuscript preparation and submission as well as submission to a national conference for presentation. There will be opportunities for a quantitative, qualitative and/or mixed method focus dependent on the student’s interests. Importantly, the student will have the opportunity to collaborate/network with our Regional and developing Provincial partners. Our students have consistently won awards for their work and produced at least one manuscript from their BSc Med experience. Anticipated Results: This investigation will be the first of its kind in prICULOS survivors following cardiac surgery and as such will represent a novel and important immediate contribution to the care of Manitobans.

All projects require a Primary and Co-Supervisor. The form may not be submitted without these fields completed. Please select the following to continue:

✔ I affirm that the primary supervisor has a minimum appointment of Assistant Professor with the Rady College of Medicine, University of Manitoba

✔ I will appoint a co-supervisor who has a minimum appointment of Assistant Professor within a College or Faculty at the University of Manitoba.

Who Should the Student Contact?

Name: Rakesh C. Arora
Address: CR3015-369 Tache Ave. St. Boniface Hospital
Phone: 204-258-1078
Email: rarora@sbgh.mb.ca

I understand that my project will not be permitted to proceed without complete ethics approvals from all stakeholders. I agree to ensure that the required ethics compliance's will be in place by the advertised deadline;

✔ Yes, I understand and agree to the terms

Please send completed form by email to: kim.ormiston@umanitoba.ca
BScMed Project Proposal

Title: Developmental Origins of Health and Disease in The Manitoba Personalized Lifestyle Research (TMPLR) Study

Supervisor: Meghan Azad, PhD
Research Scientist, Children's Hospital Research Institute of Manitoba
Assistant Professor, Pediatrics & Child Health, University of Manitoba
501G John Buhler Research Centre
715 McDermot Ave. | Winnipeg, MB Canada | R3E 3P4
+1 (204) 975-7754 | @MeghanAzad | www.azadlab.ca

Background: The Developmental Origins of Health and Disease (DOHAD) concept postulates that disruptive social and environmental exposures occurring during critical periods of development can have long term adverse health consequences. Exposures of interest include maternal nutrition and smoking in pregnancy, prenatal and postnatal stress, breastfeeding, and socioeconomic status (reflecting early childhood experiences). The TMPLR study offers a unique opportunity to investigate the independent and combined effects of early-life exposures and adult lifestyle on complex health phenotypes and disease risk.

Methods: TMPLR (www.tmplr.ca) is a $1M interdisciplinary research program recruiting 800 adult Manitobans to examine the complex interactions between lifestyle, genetics and gut microbiota in the development of chronic diseases. TMPLR participants complete extensive questionnaires about their diet and lifestyle, undergo physical activity testing and body composition measurements, and provide biological samples that are analyzed for established and emerging biomarkers of chronic disease. In addition, participants' early life experiences are documented through a maternal survey and a validated 'retrospective childhood circumstances' questionnaire. The TMPLR study has received all necessary ethical approvals and is currently underway (500 participants have been recruited as of August 2017; recruitment will continue through 2018).

This BScMed project will explore and identify early-life factors associated with the biomarkers and disease risk profiles characterized in the TMPLR cohort, in order to gain insight into the developmental origins of these health phenotypes. Multivariable regression models will be used to address questions such as: Is premature birth associated with high blood pressure in adulthood? If so, does breastfeeding 'dampen' this effect?

Anticipated Results: This study will provide new evidence identifying key early-life factors that influence long term health. Understanding the developmental origins of chronic disease is vital to designing and implementing effective prevention strategies.

Role of the student: The student will be directly involved in recruitment and data collection (eg. clinical assessment of of TMPLR participants including anthropometrics, pulse wave velocity and blood pressure). The student will also assist with administering in the TMPLR Maternal Questionnaire, and perform statistical analyses. Specific research questions and hypotheses can be tailored to the student's interest and expertise.
A descriptive study evaluating the clinical use of Obinutuzumab (GAZYVA®) including demographics, indications, CIRS, cytogenetics and prognostic markers, toxicities, adherence and financial impact and duration of treatment for frontline therapy for chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) compared to other frontline therapies.

**Background:** Chlorambucil (CLB)/obinutuzumab (O) or CLB/rituximab (R) became available in June 2015 for first line therapy in patients who were considered unfit (CIRS >6, ECOG >1 and/or renal impairment) or for patients who had previously received chlorambucil or fludarabine alone. Patients receiving obinutuzumab had to have their first treatment at CancerCare Manitoba, because of the first-treatment infusion reactions. As some patients lived some distance from Winnipeg, these cases received chlorambucil/rituximab, as first-treatment rituximab can be given at the bigger community cancer centres. Alternatively, we treated some patients with chlorambucil/rituximab initially as we felt that they would not tolerate the reactions that we initially saw with obinutuzumab. This study will describe the real life experience of obinutuzumab in the CLL clinic.

**Methods:** We will compare patient characteristics among all CLL and SLL patients who received frontline treatment between January 1, 2014 and December 31, 2017. The proposed investigations will follow a retrospective cohort design to determine patient characteristics, patterns of treatment, reported toxicities and survival measures of interest. The retrospective design will allow for the inclusion of past and current patients eligible to have received obinutuzumab as well as ensure sufficient follow-up time for survival events to occur. Patients approved for treatment with obinutuzumab between January 1, 2014 until December 31, 2017 will be enrolled and followed for a period of 10 years. To determine cost estimates, data from April 1, 2013 to March 31, 2017 is required since resource intensity weights are produced on a fiscal year basis rather than the calendar year. Finally, we will determine response by clinical remission or hematologic remission as well as the time to next treatment, progression-free, (PFS) and overall survival (OS) in this population. The N is at least 83 thus far.

**Expected results:** We will describe the population by age, gender, stage and prognostic makers including FISH within each group. We will then determine the number of cycles, dose reductions and potential toxicities including infusion reactions. We expect that prior to the change in the rate of obinotuzimab infusion in the CCMB treatment room, every patient had a reaction. We expect that discontinuations of therapy were due to toxicities opposed to death and these events were rare. For the most part most patients completed their therapy and continue to be in remission.

**Significance:** This will be the first study in Canada describing the experience using obinutuzumab in a non-trial clinical setting thus describing a true population based clinical experience. We will also determine the cost of novel agents in the CLL clinic.

**Role of student:** The student will be responsible for the retrospective chart review and descriptive statistics. The higher level statistics will be performed with the assistance of an epidemiologist.
Title: Rapid detection of antimicrobial resistant Enterobacterial outer membrane vesicles

Supervisor: Dr. Denice Bay <Denice.Bay@umanitoba.ca>

Background: By the year 2050, antimicrobial resistant bacterial infections are predicted to increase the mortality rate by an additional 20 million deaths, twice the number caused by cancer, if new strategies to detect and treat infections are not developed now. Multidrug resistant *Escherichia coli* remain one of the top blood and urinary tract infections isolated from Canadian hospitals over the past decade and are a critical priority by the World Health Organization. One of the mechanisms that *E.coli* can use to increase multidrug resistance is by shedding their outer membrane as vesicles (OMV). OMVs act defensively to absorb drugs, reducing drug entry into cells and act offensively to enhance host inflammation. The detection and isolation of OMVs from Enterobacteriaceae is laborious and currently lacks clinical guidelines. It is unclear how OMVs influence antimicrobial resistance but enhanced OMV formation is correlated to antimicrobial resistance.

Methods: The project aim will develop a rapid OMV detection assay involving vacuum filtration and fluorescent analysis to quantitatively screen multidrug resistant Enterobacteriaceae for OMV formation. A collection of 30 multidrug resistant *E.coli* isolates will be screened in 96 well microplate cultures alongside model *E. coli* strains with defined drug resistance to polymyxin and carbapenem antibiotics and antiseptics. This high throughput approach involves vacuum ultrafiltration of *E. coli* cultures, and fluorescent microplate detection of dyed lipopolysaccharides (LPS).

Anticipated Results: This project will develop a rapid diagnostic tool to detect OMVs formed by multidrug resistant Enterobacteriaceae as well as other Gram-negative infections. New tools are urgently needed to identify OMV biomarkers (lipids and proteins) to rapidly predict antimicrobial resistance phenotypes.

Role of the student: The student will grow various *E. coli* cultures in the presence and absence of antimicrobials. OMVs will be isolated from cultures using a vacuum manifold system. OMVs will be quantified in filtrates by FM4-64 dye and emission detection with a microplate reader. OMV immunodot blotting will quantify LPS. Statistical analysis of replicate drug exposed OMV preparations will be conducted by the student with supervision using excel or ‘R’ statistics.
Elucidation of the mechanism of action of a novel antibiotic targeting cell division
Bsc (Med) project 2017

CONTACT INFORMATION
Dr. Silvia T. Cardona
Associate Professor
Department of Microbiology
Department of Medical Microbiology & Infectious Disease
silvia.cardona@umanitoba.ca
cardonalab.org
@cardona_lab

SUMMARY
Resistance to antibiotics is on the rise and the antibiotic discovery pipeline is running dry, especially for Gram-negative bacteria, due to its more restrictive cell envelope. Thus, novel approaches for antibiotic discovery are urgently needed. While there are many molecules with antibacterial activity, to develop new antibiotics it is necessary to identify the targets, molecules essential for bacterial life to which the active molecules bind, causing bacterial death. Recently, we discovered a novel antibiotic molecule of broad activity, called C109. Our in vitro and in vivo studies suggest that C109 targets the cell division protein FtsZ. In this project, you will focus on investigating the effect of C109 on bacterial genetic networks with the goal of understanding uptake and global effects of this antibiotic molecule. Your work will set the basis for identifying drugs that can act in combination with C109 to increase its effectiveness.

BACKGROUND
Infectious disease is a leading cause of worldwide mortality and the ability of drugs to effectively treat many of these diseases has been decreasing due to the fast emergence of antibiotic resistance (Munita et al. 2017). As the evolution of resistance currently outpaces drug development, there is an urgent need to increase the speed of antibiotic drug discovery and drug development (Brown and Wright 2016). Given the high cost of new antibiotic developments and their short useful life, investment in the pharmaceutical industry is not justified unless solutions from academia are provided (Bush et al. 2011). The real need is that academic research provides novel and more effective antibacterial lead molecules that can be developed as antibiotics at a faster rate than new resistant bacteria arise.

In the Cardona laboratory, we have been investigating a new benzothiadiazole derivative (C109), synthesized by our collaborator Dr. Vadim Makarov, during an antibacterial discovery effort for Mycobacterium tuberculosis (Makarov et al. 2009). C109 was only slightly active against M. tuberculosis and was not pursued as an antibacterial for this bacterium. Another researcher of that group, Dr. Giovanna Riccardi discovered that C109 was active against Burkholderia cepacia complex, a group of multiple antibiotic resistant bacteria that causes lethal infections in immunocompromised individuals and people with the genetic disease cystic fibrosis. Importantly, C109 was also active against other Gram-negative and Gram-positive bacteria. C109 is a small hydrophobic molecule, which probably crosses the cell envelope of Gram-negative bacteria, through porin-mediated uptake (Wiener and Horanyi 2011). It was also demonstrated that C109 can be exported by efflux pumps as whole genome sequencing of C109 spontaneous resistant mutants of B. cenocepacia identified mutations in efflux pump genes (Scoffone et al. 2015) We also demonstrated that C109 has low toxicity to HeLa cells, cystic fibrosis pulmonary epithelial cells, and C. elegans. The low toxicity of C109 is not
Elucidation of the mechanism of action of a novel antibiotic targeting cell division

Silvia T. Cardona

Three lines of evidence point to the central bacterial cell division protein FtsZ as the target of C109: First, C109 is a broad-spectrum growth inhibitor, which suggest that its target is well conserved in bacteria. Second, the structure of C109 resembles that of the tubulin inhibitor albendazole (Perez-Serrano et al. 1995). The similarity between C109 and albendazole implies that these compounds could target distantly related homologous proteins, such as FtsZ and tubulin, respectively. Finally, a $ftsZ$ knockdown mutant (CGftsZ) was hypersusceptible to C109. Following our results, our collaborator Dr. Giovanna Riccardi expressed and purified FtsZ from $B. cenocepacia$ and assessed its enzymatic activity. In line with our in vivo evidence, C109 inhibited the GTPase and polymerization activity of the recombinant purified FtsZ.

Besides inhibiting their corresponding target proteins, antibiotics have various effects on bacterial cells, due to their interaction with secondary targets and their interaction with the cell envelope during cellular uptake. To cross the Gram-negative cell envelope, antibiotics must interact with lipopolysaccharide, membrane phospholipids and porin proteins. An example of these effects is that of daunorubicin, a tetracycline-like compound that targets protein synthesis but also intercalates within DNA causing DNA fragmentation and single strand breaks (Aubel-Sadron and Londos-Gagliardi 1984). This explains that a DNA gyrase depleted strain of $Staphylococcus aureus$ showed enhanced susceptibility to daunorubicin (Donald et al. 2009). Investigating these indirect effects of antibiotics is important as i) it can guide synergy studies to design combination therapies (Roemer and Boone 2013) and ii) it can shed light on uptake mechanisms and resistance (Jana et al. 2017). Thus, future rational designs of C109 derivatives aimed to increase its activity, solubility and bioavailability will benefit if secondary effects and mechanism of uptake is known.

The Cardona laboratory has been building genetic tools in $B. cenocepacia$ for target identification of small molecules with antibacterial activity. To build these mutant libraries, we use a transposon mutagenesis strategy that delivers a rhamnose inducible promoter into the chromosome of $B. cenocepacia$ K56-2 (Cardona, Mueller, and Valvano 2006; Bloodworth, Gislason, and Cardona 2013). If the transposon inserts within an open reading frame, then the gene is disrupted while downstream genes are placed under the control of the rhamnose-inducible promoter if they are located in the same direction of the delivered promoter. Using this method, we built a library of 1,000,000 transposon mutants and mapped the essential genome of $B. cenocepacia$ (Gislason et al, submitted) by Tn-seq (Gallagher, Shendure, and Manoil 2011). We have also screened the transposon mutant population for reduced growth in the absence of rhamnose. By isolating the clones that showed a rhamnose-dependent phenotype, we produced a library of knockdown mutants, with the rhamnose-inducible promoter inserted in front of essential genes. We propose to use our genomic libraries, to interrogate the contribution of each gene product to increased susceptibility or resistance to C109.

YOUR ROLE IN THIS PROJECT

Using the bacterial genomic libraries constructed, representing essential and non-essential genes you will analyse the genomic response of $B. cenocepacia$ to the novel antibiotic molecule C109. During the first year, you will identify genetic networks affected by C109. Specifically, you will detect loss of function mutations that i) increase resistance to C109, possibly due to reduced uptake or increased
Elucidation of the mechanism of action of a novel antibiotic targeting cell division

...i) increase susceptibility, possibly due to synthetic lethality effects with FtsZ. During the second year, you will construct loss of function mutants in selected genes and characterize their phenotypes in response to C109.

METHODS

You will expose the transposon mutant library to subinhibitory concentrations (IC30) of C109. You will analyze mutant abundance in the population exposed to C109 compared to an untreated population. To analyze individual mutant abundance, you will extract the genomic DNA of pools followed by Illumina sequencing of the transposon junctions by Tn-seq circle. To quantify the extent of depletion, amplification of the circularized transposon-genome junctions will be assessed by quantitative PCR. This will determine the number of cycles required to achieve amplification in the exponential phase, where the amplicons are proportional to the template. After quantification of the relative abundance for each mutant (normalized read count of the control/normalized read count of treatment) you will calculate log2 depletion ratios and Z-scores, which are a measure of the significance of the depletion. You will link these mutant depletion scores with their corresponding interrupted genes to produce and visualize chemical genetic interaction profiles. You will process the data with custom-made scripts and bioinformatics support from our collaborators.

To further analyze the effect of C109 on particular genetic networks you will create knockout and knockdown mutants and analyze their phenotypes using microbiology and biochemistry techniques.

The Cardona lab has genetic tools in place to create clean deletion mutants of non-essential genes and knockdown mutants in essential genes. You will be creating knockdown mutants using CRISPR interference (Peters et al. 2016). This methodology is based on expressing single guide RNAs (sgRNAs) targeting the expression of particular gene in a strain engineered to conditionally-express a nuclease-inactive Cas9 (dCas9). The inactive Cas9 binds the sgRNA and interferes with transcription of the target gene. The system demonstrated effective repression of essential genes from 3-fold to 150-fold. You will use a plasmid containing the dCas9 gene and a vector for cloning sgRNAs. You will design and express the corresponding sgRNA to shut down expression of target genes.

ANTICIPATED RESULTS

C109 is a small hydrophobic molecule and is expected to penetrate the cell envelope through porins. Alternatively, C109 could penetrate through slow diffusion across the lipid membrane. It is known that efflux pumps can excrete C109, but the regulatory components that induce efflux of C109 are unknown. We expect to find that loss of function mutations in cell envelope related genes change the susceptibility of B. cenocepacia to C109. FtsZ is part of a large macromolecular complex, called the divisome. By binding to the divisome, several proteins coordinate cell division with other essential processes in the bacterial cell, such us cell wall synthesis, chromosome replication and growth rate. We expect that the genetic networks perturbed by C109 will reflect functional interactions with the divisome. These findings will guide the design of combinations of drugs that could improve the effectiveness of C109 against pathogenic bacteria.
**Zika virus-induced proteomic effects in 3-D cell culture**

Kevin Coombs, PhD

[Kevin.coombs@umanitoba.ca](mailto:Kevin.coombs@umanitoba.ca)

**Background:** Zika virus (ZV) is a newly re-emerging mosquito-borne virus linked to rare but serious birth defects. ZV was initially isolated in Africa in 1947 but recently gained new notoriety because of its capacity to cause microcephaly in newborns. ZV belongs to the virus family *Flaviviridae*, and like most viruses in this family, is transmitted from one vertebrate to another by an invertebrate mosquito host, which, with climate change, has recently been found in Canada. ZV-host interactions remain poorly understood. Most basic studies of virus biology have been performed in monolayer (2-D) tissue culture, but cells in 3-D culture are more physiologically relevant.

**Methods:** Neuronal derived cells (oligodendrogliaoma and astrocytes) will be grown in 3-D co-culture and the capacity of ZV to grow and induce alterations in the host cell protein repertoire (proteome) determined and compared to ongoing 2-D culture conditions. Proteomic alterations will be determined by mass spectrometry- and aptamer-based methods to identify 100s of dysregulated proteins. Proteins will be mapped to specific cellular pathways and important pathways further dissected with standard biochemical, immunological and viral infectivity methods.

**Anticipated Results:** Our similar studies with 2-D cultures identified dozens of dysregulated host proteins belonging to a few key cellular master regulatory pathways. However, proteins and pathways identified in 3-D are expected to be more physiologically relevant. Further analyses of these specific pathways and how the proteins in them impinge on virus replication and pathogenesis will lead to improved diagnostics and therapies.

**Role of Student:** The student will learn how to: organize and plan experimental setup, grow and maintain host cells in 2-D and 3-D culture, grow and measure infectious virus, collect and prepare cell extracts for proteomic analysis, analyze results and design follow-up experiments.
The impact of frailty on clinical outcomes for stage IV non-small cell lung cancer patients receiving chemotherapy

**Supervisor:** Dr. David Dawe, Medical Oncologist  
**Email:** ddawe@cancercare.mb.ca

**Background:**  
Frailty is defined by increased vulnerability of patients to stressors. For cancer patients, chemotherapy is a stressor and can induce or uncover frailty. Comprehensive geriatric assessment is the best way to determine frailty, but requires special expertise and 60+ minutes per patient. Many hope briefer tools can identify frail patients. Frailty measured by the 11-item modified frailty index (mFI) is associated with morbidity and mortality in elderly surgical patients, but mFI has not been used in chemotherapy patients. We propose evaluating the association between pre-treatment mFI score with chemotherapy toxicity and survival in non-small cell lung cancer (NSCLC) patients.

**Methods:**  
Retrospective cohort study of Manitobans diagnosed with stage IV NSCLC from January 1, 2011 to December 31, 2016 who received chemotherapy as identified through the Manitoba Cancer Registry (MCR) (approx. 474). The mFI score, chemotherapy used, toxicity, performance status, cancer response, and progression date, will be derived from chart review. Demographics, cancer characteristics, and survival will be retrieved from the MCR.  
We will compare outcomes after stratifying patients as fit, pre-frail, and frail as per the mFI. Toxicity and response rates between groups will be compared using the Chi-squared test. Progression-free and overall survival will be calculated using Kaplan-Meier methods, with between group testing using the logrank test. We will then test the effect of each variable on survival using the Cox proportional hazard method. Sample size needed for 80% power to detect a 10% difference in chemotherapy toxicity (primary outcome) is 294.

**Anticipated Results:**  
We expect patients with greater frailty by mFI will have higher rates of chemotherapy toxicity and shorter survival, suggesting the tool serves to stratify patient frailty and inform decision-making prior to treatment. However, since this tool has never been evaluated in this population, any result is useful.

**Student Role:**  
Student responsible for extracting data from charts using a template. The student would be involved in data analysis and interpretation. We would expect them to participate in presenting the results of the project and contribute to manuscript preparation.
BSc.(Med) Project

Title: Developing algorithms to accurately and efficiently identify breast and colorectal cancer recurrence

Background: Cancer recurrence is the diagnosis of a second clinical episode of cancer after the first was considered cured. Cancer recurrence is an important clinical, epidemiological, and health services research outcome. Recurrence can be used to compare treatment effectiveness, measure recurrence-free survival, and plan and prioritize cancer control resources. Since cancer registries do not identify recurrent cancers, recurrence is determined using chart reviews. However, reviewing charts is time consuming and expensive. An alternative method for identifying recurrence is to use administrative health care data and electronic medical record (EMR) data. Studies that have developed and tested algorithms to identify cancer recurrence have important limitations including small sample sizes, a lack of generalizability, and limited access to additional indicators of recurrence such as imaging, radiation therapy, or hormone therapy.

The purpose of this project is to develop algorithms that can accurately capture cancer recurrence. We will use multiple sources of population-based administrative health data, structured data from the cancer patient’s EMR, and unstructured data from the health care provider’s notes in the cancer patient’s EMR. The study will be composed of two phases: an algorithm development phase and a validation phase. The algorithm development phase will consist of 1) a chart review by an experienced Cancer Registrar to define recurrence and 2) the development of recurrence algorithms using administrative health data and medical records data. The results of the chart review will be used to develop the algorithms. We will use natural language processing (NLP) to capture recurrence from the unstructured data in the health care provider’s notes in the EMR.

Methods: This study will include individuals diagnosed with stage I-III breast or colorectal cancer from 2004 to 2012. The study will be composed of two phases: a development phase and a validation phase. The development phase will consist of 1) a chart review to define recurrence and 2) the development of recurrence formulas using administrative health data and medical records data and validation. Validation will determine if the formulas developed work well in a cancer cohort that was not part of the development phase. Measures of sensitivity, specificity, PPV, negative predictive value, and their 95% confidence intervals (CI) will be calculated to determine algorithm accuracy.

Anticipated Results: The algorithms that will be developed will increase the efficiency of epidemiological and health services research on cancer treatment effectiveness and outcomes and quality of care assessments.

Role of Student: For this study, the student will work with a team of researchers who have oncology, epidemiology, and biostatistical expertise. He/she will focus on phase 1 - reviewing of charts to identify recurrence and, if time permits, working with the study team to start the algorithm development.
Title: Neoadjuvant FEC4-D4 Chemotherapy in Invasive Breast Cancer: The Manitoba Experience

Background: Neoadjuvant (or pre-operative) chemotherapy was initially studied in the setting of locally advanced, unresectable breast cancer, but also offers other advantages compared to adjuvant (post-operative) chemotherapy. These include tumour downstaging and potential breast-conservation, in-vivo assessment of tumour response, and earlier initiation of systemic therapy for high-risk phenotypes. Various chemotherapy regimens have been studied in this setting, but the optimal choice for neoadjuvant treatment remains unclear. In Manitoba, the standard neoadjuvant breast cancer regimen used for many years was FEC4-D4. This consists of eight cycles of chemotherapy (four cycles of fluorouracil-epirubicin-cyclophosphamide and four cycles of docetaxel). In contrast, most institutions using these drugs give only six cycles of treatment (FEC3-D3).

Methods: This is a retrospective observational cohort study. We will collect and describe outcome data for patients with breast cancer who received neoadjuvant FEC4-D4 between 2006 and 2016 in Manitoba. We are interested in pathologic complete response (PCR) rates, recurrence and survival events, and toxicity (adverse events). The goal is to compare this data to a similar cohort of Ontario patients who received FEC3-D3 over the same time period. Continuous variables will be compared between treatment groups using the Wilcoxon Rank Sum test. Categorical variables will be compared using the $\chi^2$ statistic. Time-to-event analyses will be performed separately for overall survival and recurrence-free survival. Subgroup analysis will be performed based on breast cancer subtype.

Anticipated Results: Findings from this study will contribute to the growing literature surrounding optimal neoadjuvant systemic therapy for breast cancer. Manitoba is in a somewhat unique position of having adopted this non-standard regimen and used it exclusively for many years. As such, the Manitoba experience will contribute valuable information as to the optimal number of treatment cycles for these drugs.

Student Role: The student will work primarily within CancerCare Manitoba, and will have a broad exposure to all steps of conducting a successful retrospective cohort study. They will gain exposure to research ethics board submission (prior to the summer experience), and will help design a data collection form, and conduct a chart review for relevant information. They will then summarize the data and help to analyze the results with appropriate statistical support. They will also have the opportunity to form connections with researchers and clinicians in Ontario. We anticipate the student will present these results at a national oncology conference (e.g. CAMO) with subsequent publication in a peer-reviewed scientific journal.

Primary Supervisor:

Dr. Danielle Desautels  
Medical Oncologist, CancerCare Manitoba  
Assistant Professor, University of Manitoba Rady Faculty of Health Sciences  
Email: ddesautels@cancercare.mb.ca  
Phone: (204)787-1815
Strategies to enhance benefits of allogeneic stem cell therapy for cardiac regeneration

The stem cell therapy has emerged as novel treatment option for heart disease as stem cells can differentiate to cardiac cells and replace the dead cells. Bone marrow derived allogeneic (unrelated donor) mesenchymal stem cells (MSCs) from young healthy donors are considered to be the ideal candidate cell type for cardiac repair. The initial clinical trials reported that allogeneic MSCs were safe to the patients as no side effects were observed, and transplanted cells improved the heart function. However long term fate of transplanted cells in these clinical trials was not clear. We recently demonstrated that allogeneic MSCs alleviated the host immune response and survived early after injection in the ischemic myocardium, but cells were rejected late after implantation in the heart. Thus there is a need for an in-depth investigation of immune properties of allogeneic MSCs under ischemic or hypoxic conditions before we take these cells to the clinic for cardiac repair. The immunoprivilege of MSCs is reported to be established by the downregulation of major histocompatibility complex (MHC)-II molecule. Our studies demonstrated that MHC-II expression increased in MSCs after exposure to hypoxia or ischemic conditions which was associated with a loss of immunoprivilege and the rejection of allogeneic MSCs in the heart. However, the underlying mechanisms for this hypoxia induced immune-switch in MSCs are unknown and will be investigated in the current proposal. Outcome of these studies will help us in developing the strategies to preserve immunoprivilege of allogeneic MSCs, prevent the rejection of transplanted cells in the ischemic heart and enhance the benefits of allogeneic MSCs therapy for cardiac regeneration.
Background
Rheumatoid arthritis (RA) is known to exhibit familial clustering, particularly in Indigenous North American (INA) populations. It is also known that RA has a prolonged preclinical phase where immune abnormalities develop prior to detectable clinical manifestations. In order to develop a better understanding of this phase, our research group has established a cohort of INA RA probands and the first degree relatives (FDR) of these RA patients who are being followed longitudinally for RA onset.

The INA population has a high frequency of type II diabetes, metformin is typically first-line therapy for diabetes. Although no direct association between diabetes and RA has been detected, it has been shown that metformin modulates the metabolic profile of T and B lymphocytes, and ameliorates murine models of autoimmune disease.

Hypothesis
Immune abnormalities leading to RA, such as development of autoantibodies and autoreactive lymphocytes, are less frequent in individuals taking metformin.

Methods
For the past 10 years, our group has been longitudinally following a cohort of 564 FDR of INA RA patients for disease onset. On yearly study visits, clinical data are gathered, including diabetes status and treatment, and biospecimens are obtained. A conservative estimate is that 131 FDR have a diagnosis of diabetes, most of whom are treated with metformin. Study procedures are approved by U of M Bioethics Board, and are governed by written agreements with INA study communities.

It is proposed that over the course of the first summer, the student will extract RA patients and FDR taking metformin from the study database, and then match them for age and gender with RA patients and FDR who are not taking this drug. The prevalence of autoantibodies and other circulating immune abnormalities will be evaluated and compared using techniques such as ELISA. During the second summer, the effects of metformin on lymphocyte activation and production of autoantibodies will be examined in vitro.

Anticipated Results
Demonstration that metformin is associated with lower frequency of circulating autoantibodies and autoreactive T and B cells, based on metabolic regulation of the autoreactive cells.

Contact
Dr. Hani El-Gabalawy MD FRCPC, Professor of Medicine and Immunology
Hani.elgabalawy@umanitoba.ca
204-787-2208
IMPACT OF ADJUVANT CHEMOTHERAPY INITIATION, COMPLETION OR DISCONTINUATION ON RECURRENCE AND SURVIVAL RATES IN PATIENTS WITH COLON CANCER

Primary Supervisor: Dr. Tunji Fatoye, Department of Family Medicine, UMan (tfatoye@sogh.mb.ca)
Co-Supervisor: Dr. Piotr Czaykowski, CancerCare Manitoba

BACKGROUND: Adjuvant chemotherapy (AC) following surgery for colon cancer can reduce recurrence rates and improve survival. Although efficacy has been proven, toxicity can be an issue and many patients are unable to complete the prescribed number of cycles of AC. The decision to discontinue AC can be difficult and the extent to which it happens, factors associated with it, and its impact on patient outcomes is unclear. Currently, providers do not have the knowledge to fully support patients who fear that prematurely discontinuing AC will negatively impact their chance for disease-free survival.

OBJECTIVE: To determine the rate of AC discontinuation among patients with colon cancer in Manitoba and compare the rate of recurrence and survival between patients who completed versus discontinued any of the standard AC regimens.

METHODS: Patient encounters will contextualize findings from a retrospective analysis of patient clinical records from the provincial cancer registry (CancerCare Manitoba), charts and health administrative databases. The study will evaluate the rates of AC initiation and discontinuation, identify patient characteristics associated with premature discontinuation and assess its impact on patient recurrence and mortality.

ANTICIPATED RESULTS: Evaluating the rate of recurrence between those who complete AC versus those where AC was discontinued is important to add new information on an issue that is of great importance to the patient population affected and their physicians providing care. It is anticipated that the results will be of broad interest to providers, appealing to oncology specialists and equally primary care providers, who provide ongoing support throughout oncology care and later, recurrence surveillance and follow-up after treatment.

DESCRIPTION OF STUDENT ROLE: First term: The student will develop skills to organize, interpret and understand clinical records and extract data relevant to rates of AC initiation and discontinuation. A brief review of the relevant literature will provide a basic background and context for ongoing work. Second term: The student will analyze results, and contextualize findings in preparation for drafting manuscripts for publication as a co-author. Overall: The student will have the opportunity to network and collaborate between faculty within CancerCare Manitoba and the Department of Family Medicine. Additionally, the student will learn to assess clinical data, with the goal of translating the knowledge learned towards clinical care.
Abstract for BSc Med Student:

**The impact of LAG3 on lymphocyte susceptibility to HIV infection**

HIV remains a major global health problem with over 37 million people currently infected. Antiretroviral therapy (ART) has transformed HIV from a severe acute disease to a chronic one. Although ART suppresses most HIV replication, it does little to restore the immune dysfunction caused by the virus. One major aspect of this dysfunction is immune exhaustion, which is caused by persistent activation of lymphocytes – leading to their functional impairment. Several proteins are expressed on exhausted cells which contribute to their functional deficiency. Expression of one such protein called LAG3 is increased during HIV infection and is associated with worse disease. Furthermore, cells expressing LAG3 are twice as likely to be latently infected with HIV as their LAG3− counterparts.

We hypothesize that LAG3 expression impacts susceptibility of CD4+ lymphocytes to HIV infection.

In order to accomplish this, we will use the lentiviral core facility to create a lentiviral vector encoding LAG3. Using this vector, we will transduce T cells with LAG-3 and perform HIV infection assays in culture. We will then measure number of HIV infected cells and amount of HIV produced.

**Research plan**

Summer 1: Obtain LAG3 lentiviral vector. Test the vector by transducing T cells and measuring LAG3 expression by flow cytometry.

Summer 2: Perform in vitro infection assay of transduced and non-transduced cells and measure degree of infection.
Real-world experience with procarbazine, CCNU and vincristine (PCV) chemotherapy after radiotherapy (RT) for grade II and III gliomas

Background

Diffuse gliomas are the most common malignant brain tumors in adults. The use of PCV for treatment of grade 2 or 3 gliomas has increased following the publication of several phase 3 trials which demonstrated an overall survival advantage for PCV when compared to RT alone. The interim results did not show a survival difference, and were presented when temozolomide (TMZ) was discovered to be effective treatment for glioblastoma. As a result, many institutions favor the use of TMZ for these tumors. PCV brings several challenges with implementation, including a significant side effect profile, drug interactions, and supply chain issues. These concerns may reduce the use of PCV as first line therapy despite level I evidence supporting its efficacy.

Methods

We will retrospectively review all patients with both grade II and III gliomas who received PCV after RT as first line treatment. Data will be collected from electronic and paper charts, the Manitoba Cancer Registry, and the CancerCare Manitoba pharmacy database. The outcomes of interest will be rates of toxicity, dose delays, hospitalization, number of cycles completed and progression free survival (PFS). Demographics, molecular marker status and data on quality of life will also be gathered. These results will be compared to those recorded in the phase 3 trials.

Expected results

Based on studies in other malignancies, we anticipate the toxicity rates will be higher when compared to the clinical trial setting, with similar PFS. We expect the toxicity encountered to largely be manageable as an outpatient with minimal long term sequelae. The results will guide ongoing use of PCV chemotherapy for the indications outlined in the clinical trials.

Role of the student

The student will gain experience in conducting a retrospective observational research study. They will help submit the necessary documentation for study approval, and participate in discussions regarding study design and implementation prior to the summer experience. The student will conduct data collection and chart review, followed by data summary and analysis with appropriate statistical support. We anticipate opportunities to present the findings at local and national research meetings, with subsequent publication in a peer reviewed journal.

Primary Supervisor

Dr. Craig Harlos
Medical Oncologist, CancerCare Manitoba
Assistant Professor, University of Manitoba Rady Faculty of Health Sciences
Email: charlos@cancercare.mb.ca
Phone: (204) 787-2128
Explore the effects of diet and genetics on inflammatory bowel disease pathogenesis

**Background:** Inflammatory bowel disease (IBD) is a complex disorder affecting 0.5% of Canadians. Previous studies have indicated that some IBD patients show mild disease activity and do well with basic medication, but many others exhibit a more severe disease trajectory with growth failure, continued active gastrointestinal symptoms, and the eventual development of disease complications requiring surgery. Environmental factors, such as diet, are also critical components of disease susceptibility. To decide an appropriate course of treatment, it is important to investigate core environmental (diet) and genetic features and correlates of IBD phenotypes in elucidating the sources of heterogeneity in IBD patients.

**Methods:** We have generated genome-wide genetic data for approximate 280 IBD patients from the Manitoba IBD Cohort Study. More than 5,000 copy number variations were identified from the genetic data of these patients. Food avoidance and sugar intake data of the patients were also collected. We will perform the associations of various dietary components and IBD genetic risk in genetically susceptible IBD models.

**Anticipated Results:** Improve understanding of how diet combining with IBD genetic risk factors influences IBD behavior and promotes disease.

**Role of the Student:** The student's roles will include: 1) organizing clinical, diet and genetic data; 2). performing basic data analysis; 3) interpreting the diet, genetic and clinical data analysis results; 4). making public presentation(s); and 5) writing a research paper as a first author. The student will be working closely with supervisors and a postdoctoral fellow in bioinformatics.

**Supervisors and Contact Information:** Dr. Hu's lab (http://www.hu-bioinformaticslab.org) focuses on translational medicine research in bioinformatics and statistical genetics. Dr. Bernstein's lab focuses on IBD's clinical research. The student will be trained to understand and perform some basic diet, genetic and clinic data analysis using available tools and translate the knowledge towards IBD clinical care.

Pingzhao Hu, Ph.D., Assistant Professor (Bioinformatics/Statistical Genetics)
Max Rady College of Medicine, Rady Faculty of Health Sciences
Department of Biochemistry and Medical Genetics, Room 308 - Basic Medical Sciences Building, Tel: 1-204-789-3229, pingzhao.hu@umanitoba.ca
Flaxseed in the mitigation against anthracycline and trastuzumab mediated cardiotoxicity  
(FANTAM study)

**Background**
Cancer and cardiovascular disease are the leading causes of mortality in Canada, accounting for over 120,000 deaths on an annual basis. With the significant advances in the treatment of cancer disease over the past three decades through a combination of lifestyle modification, pharmacological therapy, and surgical intervention, overall survival has increased accordingly. Complementary and alternative medicine approaches are widely used by cancer survivors in an attempt to reduce overall disease burden and prevent recurrence. Amongst functional foods, which have physiological benefits beyond their basic nutritional functions, up to 30% of women use flaxseed (FLX) in the management of their underlying breast cancer. Despite our increased understanding of the potential role of FLX in preventing cancer development, little is known on its potential cardioprotective effects against cardiovascular disease in the breast cancer setting.

**Objective**
To investigate whether the prophylactic administration of FLX will be cardioprotective in a chronic *in vivo* murine model of chemotherapy induced cardiotoxicity.

**Methods**
To explore the role of FLX in protecting the heart from the damaging effects of Doxorubicin (DOX) and Trastuzumab (TRZ), we will use a female animal model where mice will receive a combination of the various possible drug combinations. Over a 6 week time period, female mice will be fed either milled FLX or one of its components including alpha-linolenic acid (ALA) or lignans. Throughout the course of the study, the mice will be exposed to DOX, TRZ, or a combination of the two anti-cancer drugs and imaged on a weekly basis using ultrasound to evaluate for changes in the heart structure and function. At the end of the study, histological and biochemical studies will be performed to study the potential cardioprotective mechanism(s) of FLX in this setting.

**Anticipated results**
Our overall expectation of this research study is that the cardiotoxic side effects of common anti-cancer drugs will be attenuated by the prophylactic administration of FLX.

**Role of the student**
The BSc Med student will be exposed to animal models of chemotherapy mediated cardiotoxicity, acquisition and analysis of murine echocardiograms, histological analysis using light and electron microscopy, biochemical studies, and statistical analysis.

All projects require a Primary and Co-Supervisor. The form may not be submitted without these fields completed.

Please select the following to continue:

- ✔️ I affirm that the primary supervisor has a minimum appointment of Assistant Professor with the Rady College of Medicine, University of Manitoba
- ✔️ I will appoint a co-supervisor who has a minimum appointment of Assistant Professor within a College or Faculty at the University of Manitoba.

Who Should the Student Contact?

Name: Dr. Davinder S. Jassal
Address: Rm Y3531-Bergen Cardiac Care Centre, SBGH, 409 Tache Avenue, Winnipeg, Manitoba
Phone: 204-237-2023
Email: djassal@sbgh.mb.ca

I understand that my project will not be permitted to proceed without complete ethics approvals from all stakeholders. I agree to ensure that the required ethics compliance's will be in place by the advertised deadline;

- ✔️ Yes, I understand and agree to the terms
Investigating the Neuroprotective Role of Neuregulin-1 in Traumatic Spinal Cord Injury

Introduction and Rationale: Spinal Cord Injury (SCI) results in significant cell death and tissue degeneration causing complete loss or dysfunction of sensory, autonomic, and motor function in patients at and below the site of injury. To date, no effective treatment option has been identified for SCI, and there is substantial incentive for developing regenerative medicine therapies for this condition. Extensive preclinical research from our group and others has convincingly shown the promise of neural stem cell (NSC) therapies for SCI. Indeed, based on these preclinical findings, NSC transplantation has moved to clinical trials in recent years. Initial outcomes of these trials indicate that NPCs are safe and hold promise as a treatment strategy for SCI, however, their benefit for neurological recovery is rather modest. This is mainly attributed to the limited survival, integration and differentiation of engrafted NSCs in the impermissible milieu of SCI, establishing a need for development of combinatorial strategies to augment transplant survival and cell replacement in SCI.

We have made the original discovery that both SCI and multiple sclerosis result in acute and permanent depletion of Neuregulin-1 (Nrg-1), a critical factor for NSC differentiation and survival. In a preclinical model of traumatic SCI, we demonstrate that Nrg-1 therapy promotes endogenous replacement of myelin-forming oligodendrocytes and fosters a positive immune response that culminates in improved neurological recovery. Importantly, our initial stem cell transplantation studies indicate that Nrg-1 co-therapy can optimize the long-term survival of engrafted NSCs in SCI suggesting a neuroprotective role for Nrg-1 that needs further elucidations.

Main Objective: In this translational project, we will evaluate the neuroprotective effects of Nrg-1 therapy on the survival and function of NSCs following injury using parallel in vivo and in vitro models. We will administer human recombinant Nrg-1 to rats with contusive SCI at the time of NSC transplantation by systemic delivery. In vitro, primary adult spinal cord derived NSCs will be exposed to SCI-relevant conditions such as glutamate excitotoxicity and hypoxia. Using an array of advanced cellular, molecular and imaging techniques, we will assess the efficacy of Nrg-1 in optimizing NSC survival as well as their ability for cell differentiation and migration under injury conditions. We will also evaluate neurological benefits of NSCs transplantation and Nrg-1 co-therapy following SCI.

Impact and translational feasibility: Nrg-1 is a drug approved by the US Food and Drug Administration (FDA) that has been used in a Phase II trial for cardiac dysfunction meaning that it is safe for patients. Importantly, Nrg-1 has ideal pharmacokinetics enabling its entry to the brain and spinal cord tissue via the blood-brain-barrier. Thereby, if our therapeutic work shows beneficial effects, Nrg-1 has high translational feasibility as a new therapeutic target for SCI.

Role of the Med II Student Researcher: The Med II student would have the opportunity to work closely with our research team to contribute to this comprehensive project. The student will be trained by senior member of our team to participate in cellular and molecular assessments related to the proposed in vitro studies. If interested, the student will also have the opportunity to observe our SCI procedures in vivo. The student will be credited for the data they provide for the project. Our laboratory is located in the Regenerative Medicine Program in the Rady Faculty of Health Sciences.

Contact information:

Dr. Soheila Karimi
Regenerative Medicine Program
629-Basic Medical Sciences Bldg.
Max Rady College of Medicine
Email: Soheila.Karimi@umanitoba.ca, Tel: 204-272-3109
Lab homepage: http://home.cc.umanitoba.ca/~karimis/
Development and evaluation of new therapeutic targets for multiple sclerosis

Rationale: Multiple sclerosis (MS) is a progressive autoimmune condition of the central nervous system (CNS) that is characterized by immune-mediated demyelination (loss of myelin sheath around axons). MS affects millions of individuals worldwide, with the majority being young adults. Canada has a high prevalence of MS with nearly 23.9 per 100,000 population. While functional impairments are reversible at early stages of MS due to spontaneous myelin repair, with disease progression and re-occurrence of autoimmune demyelination, axons degenerate permanently resulting in irreparable damage to the neural circuitry and neurological deficits.

Currently no effective treatment strategy has been identified for MS, and development of clinically relevant therapies is critically needed. Our recent investigations in a relevant preclinical model of MS (Experimental Autoimmune Encephalomyelitis, EAE) has uncovered a link between dysregulation of Neuregulin-1 (Nrg-1) and the imbalanced immune response and impaired remyelination in MS lesions. Nrg-1 is an essential growth factor for development and function of the nervous system. Importantly, in MS patient samples, we have also verified the same Nrg-1 pathology showing the clinical relevance of our preclinical findings. Our ongoing therapeutic work in the EAE model shows the promise of Nrg-1 therapy in attenuating demyelination and fostering a pro-regenerative immune response in progressive MS lesions.

Main objective: In this translational project, we will extend our initial discoveries to further evaluate the therapeutic benefits of Nrg-1 in recovery from EAE. We will administer human recombinant Nrg-1 through systemic delivery to the EAE mouse at different stages of the disease, and assess the efficacy of Nrg-1 therapy using a variety of advanced cellular, molecular and imaging techniques in vivo and in vitro. We will also evaluate neurological outcomes of Nrg-1 treatment.

Impact and translational feasibility: Neuregulin-1 is a drug approved by the US Food and Drug Administration (FDA) meaning that it is safe for patients. Additionally, Neuregulin-1 has ideal pharmacokinetics enabling its entry to the brain and spinal tissue via the blood-brain-barrier. Thereby, if our therapeutic work shows beneficial effects, Neuregulin-1 has high translational feasibility as a new target for MS.

Role of the BSc MED Student Summer Researcher: The BSc Med student would have the opportunity to work closely with our research team to contribute to this comprehensive project. The student will be trained by senior member of our team to participate in cellular and histopathological assessments of spinal cord tissue and tissue culture samples. The student will be credited for the data they provide for the project. Karimi’s laboratory is supported by the Multiple Sclerosis Society of Canada. The laboratory is located in the Regenerative Medicine Program in the Faculty of Medicine. Lab homepage: http://home.cc.umanitoba.ca/~karimis/

Contact information:
Dr. Soheila Karimi

Regenerative Medicine Program
629-Basic Medical Sciences Bldg
745 Bannatyne Ave., Winnipeg MB R3E 0J9
Email: Soheila.Karimi@umanitoba.ca
Tel: 204-272-3109
**Background**

Every 10 minutes a baby is born with a hole in their diaphragm and abnormal lung development. This is called congenital diaphragmatic hernia (CDH). One third of these babies will die because of their abnormal lung development. In our laboratory we study the abnormal lung development in CDH and we aim to develop a prenatal therapy using non-coding RNAs, such as circular RNAs.

**Methods**

We use a rat animal model for CDH based on the teratogenic effects of the herbicide nitrofen. We have discovered that some circRNAs are higher or lower expressed in the abnormally developed lungs of CDH rats compared to control. We will use RT-qPCR and *in situ* hybridization to investigate when and where the circRNAs are expressed in lungs of control and nitrofen-induced abnormal lungs.

**Anticipated results**

As a pilot study we performed a microarray screen of circRNAs in control and nitrofen-induced abnormal lungs. We found that some circRNAs were up-/downregulated up to ten times in the nitrofen lungs. We anticipate to identify a specific temporal and spatial expression pattern of these circRNAs in both the normal and abnormally developed nitrofen lungs. This will help us to better understand the role of non-coding RNAs in lung development and the results will guide the development of a prenatal therapy for abnormal lung development and CDH.

**Role of the student**

The student will be working together with a graduate student and/or postdoctoral fellow on this project. The student will learn about normal and abnormal lung development and CDH. The student will learn to perform the described experimental techniques independently.

For more information contact Dr. Richard Keijzer, pediatric surgeon-scientist, Department of Surgery and Children’s Hospital Research Institute of Manitoba

Richard.Keijzer@umanitoba.ca
2049757781
HIV associated community acquired pneumonia remains the most common cause of hospital admission in Manitoba. Considering the high burden of disease, low diagnostic yield of current diagnostic strategy, improved methods are needed to accurately diagnose and treat pneumonia in HIV infected individuals. Much is known regarding “typical” pneumonia, in contrast, very little information is known about the role of atypical bacterial culprits including *Legionella* spp. in causation and consequences of pneumonia among HIV infected patients.

*Legionella* are intracellular pathogens that account for approximately 15% of all pneumonias in the general population. In immunocompromised patients, such as those with HIV, *Legionella* infections occur at higher rates and are estimated to account for approximately 20% of all HIV-associated pneumonias. In addition, studies have shown that highly immunosuppressed HIV-infected individuals often present with a more severe clinical presentation than their immune competent counterpart. Since HIV targets CD4 T cells resulting in decreased numbers and altered function of these cells, the ability to mount an effective Th1 response is greatly hindered, resulting in a more severe *Legionella* infection.

Diagnosing HIV-associated *Legionella* pulmonary infections remains challenging. Polymerase chain reaction (PCR) methods, targeting the *Legionella mip* gene, are considered to be more specific, sensitive and rapid compared to traditional diagnostics (approximately 15% increased yield vs culture), however, in developing nations, these automated techniques are not readily available. Earlier this year, in a pilot study we conducted, we found that up to 34% of HIV-infected individuals admitted with community-acquired pneumonia were also positive for *Legionella*. Moreover, we found that HIV-associated *Legionella* infections were often associated with *P. jirovecii* or *M. tuberculosis* co-infections. A potential explanation for these co-infections may be speculated based on the pathogenesis of these microbes. Given that elimination of *Legionella* infection from the host is primarily reliant on a Th1 response, namely interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin (IL)-12, IL-18, as well as the cells that produce these types of cytokines, it is logical to assume that infections that decrease production of these host factors, such as those associated with *M. tuberculosis* or *P. jirovecii*, will lead to enhanced *Legionella* persistence.

Although the host inflammatory response has been a focus of many studies, currently our understanding regarding the pathogenesis of and the host lung immune response to *Legionella*, both *L. pneumophila* and *Legionella non-pneumophila* species, is incomplete.

Pneumonia is the most common cause for admission among HIV infected individuals in Manitoba and improving diagnostic tests and understanding of the role of legionelliasis in coinfection, disease severity and lung inflammation can translate to targeted therapy and improved outcomes.

Student will perform PCR based diagnostics and measure inflammatory cytokines associated with Legionella infection; will participate in statistical analysis.

Anticipated results: improved molecular diagnostics for legionella and insights into the inflammation caused by legionella infection.
Introduction: Influenza viruses are a threat to global public health and result in ~500,000 deaths each year from annual and occasional unpredictable pandemics. Influenza infections are associated with high rates of morbidity and mortality within vulnerable populations including infants, the elderly, and those with chronic diseases. Secondary bacterial infections frequently complicate influenza infections during both seasonal outbreaks and pandemics resulting in increased morbidity and mortality. It is estimated that >95% of severe illnesses and fatalities that occurred during the 1918 influenza pandemic, which resulted in ~50 million deaths globally, were complicated by secondary bacterial infections. Although influenza infections commonly result in self-limited pneumonia, they can result in acute respiratory distress syndrome (ARDS), a potentially fatal complication. Damage to the epithelial-endothelial barriers of pulmonary alveoli is a major contributor to ARDS resulting in gas exchange abnormalities, fluid leakage and respiratory insufficiency. These deleterious manifestations likely involve both pathogen- and host-mediated mechanisms resulting in the loss of barrier function. The overall objective of this project is to characterize the molecular events that underlie the clinical sequelae of severe influenza A virus (IAV) infections that are complicated by methicillin-resistant Staphylococcus aureus (MRSA) co-infection in a tissue culture model of the alveolar-capillary barrier.

Methods: Our investigations will focus on characterizing the molecular mechanisms associated with loss of barrier function in pulmonary alveoli. We will establish a co-culture model of the human alveolar-capillary barrier with co-cultured primary alveolar epithelial and pulmonary microvascular endothelial cells and determine pathogen replication kinetics and route of invasion at the alveolar-capillary barrier during IAV-MRSA co-infection. Further, we will characterize alveolar-capillary barrier dysfunction and bacterial virulence factor responses during IAV-MRSA co-infection. Lastly, we will assess the relation between dysregulated host cell signaling responses and alveolar-capillary barrier permeability during IAV-MRSA co-infection by kinome analysis.

Anticipated Results and Student Roles: This proposal will provide critical knowledge regarding the molecular mechanisms of severe IAV-MRSA co-infections within the lower respiratory tract. Through our physiologically-relevant cell culture model of the alveolar-capillary barrier we will identify the roles of pathogen (viral and bacterial) replication kinetics, pathogen transmigration/route of invasion, bacterial virulence factor expression and host cell signaling dysregulation to the severity of IAV-MRSA co-infections. The student will be expected to participate in training and performance all aspects of the described research. These will include: i) growth and maintenance of alveolar-capillary barrier co-cultures; ii) viral/bacterial infections and quantification of replication kinetics; iii) capillary barrier permeability assays; iv) pathogen transmigration assays; iv) analysis of bacterial virulence factor expression by RT-qPCR; and v) performance of kinome analysis with kinome peptide arrays.

Jason Kindrachuk
SELECTIVE KNOCKDOWN OF MISFOLDED SOD1 AS A THERAPY FOR ALS

Over the past two decades a major breakthrough in ALS research is the discovery that mutations in the gene SOD1 are a cause of familial ALS. Strong evidence supports that the FALS-linked SOD1 variants are readily susceptible to posttranslational modifications, and subsequently become misfolded. Accumulation of the misfolded SOD1 triggers a toxic cascade leading to motor neuron degeneration. Studies also show that the WT human SOD1, when modified post-translationally, undergoes aberrant conformational changes and acquires the same toxic functions that are observed for FALS-associated SOD1 variants. Misfolded SOD1 is thus at the center of ALS pathogenesis and a common toxic factor to a subset of both familial and sporadic ALS. Therefore, selective knockdown of misfolded SOD1 could be a cure for ALS. This project attempts to tackle selectively the misfolded form of SOD1. Building on a peptide-directed lysosomal protein degradation strategy that we reported previously (Patent application number: WO 2014047741 A1), we have recently succeeded in selectively knocking down of misfolded SOD1; Insertion of the CT4 epitope of Derlin-1 into our chaperone-mediated autophagy system resulted in a rapid and selective degradation of misfolded SOD1. Here we propose experiments to determine the efficacy and specificity of the CT4-directed lysosomal degradation on misfolded SOD1 in vitro and in vivo, and perform preclinical (non-GLP) studies on the pharmacological characteristics of the peptide towards an Investigational New Drug (IND) application and phase I/II clinical trials.

Our hypothesis is that the CT4-directed and chaperone-mediated autophagy pathway selectively degrades misfolded SOD1, and is a cure for ALS. To test this hypothesis, we have three objectives:

1) We will determine the efficiency and specificity of the CT4-directed and chaperone-mediated autophagy pathway in knocking down of misfolded SOD1 derived from constitutively expressed SOD1 mutants in primary cultures of neurons.

2) We will determine the therapeutic efficacy of the CT4-directed and chaperone-mediated autophagy pathway in mouse models of ALS. Using the G93A and the G37R mouse lines, we will determine the efficiency of the TAT-CT4-CTM on degradation of misfolded SOD1 when given systemically, and determine the therapeutic efficacy of the TAT-CT4-CTM peptide in preventing the onset of ALS and in modifying the disease process when used before and after the onset of ALS.

3) We will examine the pharmacological characteristics of the therapeutic peptide TAT-CT4-CTM towards an Investigational New Drug (IND) Application, including the pharmacokinetics in plasma and peptide accumulation in the brains of mice administered intravenously, and its pharmacological characteristics.

Successful completion of the project will likely advance the TAT-CT4-CTM to an IND application and phase I/II clinical trials.

This 5-year project embodies a wide range of advanced knowledge in neuroscience and cutting-edge techniques, and is funded by Brain Canada/ALS Canada. The BSc(Med) student will work on a selected portion of the project yet have ample opportunities to interact with our research associates, graduate students and postdoctoral fellows.

Contact: Dr. Jiming Kong, Professor, Department of Human Anatomy and Cell Science, College of Medicine, University of Manitoba. Phone: 204-9775601; Email: Jiming.Kong@umanitoba.ca
**Background**: Whole Genome Sequencing (WGS) is becoming a standard tool for typing of certain pathogens which may be related in an outbreak or already the subject of active surveillance nationally. We propose a pilot project to study some *Corynebacterium diphtheriae* strains which had been recovered in Manitoba (possibly other provinces), to establish if isolates are related at a genomic level.

**Methods**: **Bacteria**: standard NML methods for WGS and analyses will be employed to study strains, all of which have been characterized by the NML’s Special Bacteriology laboratory (SBL) to genus and species and for the presence/absence of diphtheria toxin expression.

**Statistical Methods**: not applicable

**Epidemiological Methods**: We plan to recruit epidemiologists to do a simple review of DSM referrals of Manitoba isolates to establish if there are any commonalities among patients who had had *C. diphtheriae* infections. Several have already been approached about this project.

**Sample Size**: ~60-70 strains of *C. diphtheriae* from Manitoba have been characterized since 2001, of which 23 have had MLST done (unpublished). As comparators, numerous draft genomes of *C. diphtheriae* are already deposited in the NCBI. To date however, only two NML strains of *C. diphtheriae* from this province have had WGS done (from a total of 5 isolates subjected to WGS).

**Anticipated Results**: We hope to establish 1) use of WGS as a typing tool 2) ascertain if one or a few predominating genomic types are in circulation or if strains are largely unique 3) publication of results

**Role of the Student**: Some of the science work will be done at the SBL in 2017-2018 (limitation being resources for performing WGS). We expect that the student will assist with WGS data analysis after training and assist with cross linking lab results to epidemiological data.

**Co-Supervisor**: Kathryn Bernard. 204-789-2135 kathy.bernard@phac-aspc.gc.ca
Congenital surgical anomalies long-term follow-up study – link with Manitoba Centre for Health Policy

Background
In 2016, we created a database of patients with any of eight congenital surgical anomalies treated at Health Sciences Centre over the past twenty-five years. The data includes: patient demographics, prenatal history, maternal risk factors, surgical management and short-term outcomes. Our database allows us to assess short-term outcomes but we cannot determine long-term outcomes.

The Manitoba Centre for Health Policy (MCHP) is a research unit at the University of Manitoba. The MCHP has a repository of databases from publically-funded services including health care, social services and education. The MCHP data can be linked to other research data to identify factors influencing health and socioeconomic outcomes.

We will link our database to the MCHP repository and perform a retrospective case-control analysis with the following objectives:
1. Identify maternal factors associated with an increased incidence of congenital anomalies.
2. Compare the long-term outcomes of patients with a surgical anomaly to age-matched controls.
3. Determine patient and maternal factors of children with anomalies that affect long-term outcomes.

Methods
Our cohort consists of 700 patients with congenital diaphragmatic hernia, congenital lung lesions, esophageal atresia, gastroschisis, Hirschsprung’s disease, imperforate anus, intestinal atresia or omphalocele. We will construct the 10:1 control population from date-of-birth matched newborns identified in the Manitoba Insurance Registry database.

Ethics approval and approval to link with MCHP have been submitted. Funds have been secured through the Child Health Research Institute of Manitoba to cover the cost of accessing the MCHP databases.

Anticipated results
We hypothesize that there are demographic, medical, educational and socioeconomic differences between mothers of, and children with, congenital surgical anomalies compared to controls.

Role of the student
The student will be responsible for generating and analysing the data produced by the link with MCHP. Analysis will be conducted with the assistance of a MCHP research assistant and the pediatric general surgeons, Drs. Keijzer, Morris and Lum Min.

Contact
Dr. Suyin A. Lum Min
slumming@exchange.hsc.mb.ca
Magnitude and spectrum of antibodies targeting HIV protease cleavage sites and their correlation with resistance to HIV-1 infection in the Pumwani Sex Worker cohort

**Background:** The Pumwani Sex Worker cohort was established in Nairobi, Kenya in 1985 as an observational cohort study of the immunobiology and epidemiology of sexually transmitted infections (STI)12-15. It is an open prospective cohort located in the heart of Pumwani slum. The patients enrolled in the cohort had been followed biannually from the cohort establishment to 2014. Through more than 20 years of biannual biological and clinical follow ups, a sub-group of women who are resistant to HIV-1 infection have been identified. These women remain seronegative and PCR negative for HIV-1 for prolonged periods despite heavy exposure to the virus through active sex work. Recently we have detected the existence of antibodies targeting HIV-1 protease cleavage sites (PCS) in a group of HIV resistant women. The existence of the anti-PCS antibodies indicates that these women have been exposed to HIV through high risk sex work. **However, do these anti-PCS antibodies play a role in protecting these HIV resistant women from HIV acquisition?** Since no HIV viruses have been detected in these women there is a possibility that these anti-PCS antibodies are one of the contributing protective factors. Although the role of these anti-PCS antibodies in protection from HIV acquisition and the related mechanisms remain to be determined, the existence of these anti-PCS abs in all >300 sex workers we have examined, suggest that they are relatively easy to induce. If the anti-PCS abs do contribute to the protection from HIV infection in these women and are easy to induce, then it will provide another anti-HIV vaccine strategy.

**Methods:** The proposed study will analyze anti-PCS antibodies in historical collections of plasma samples of 120 HIV resistant women (3265 samples collected from 1985 to 2009, and 250 HIV seroconverters (851 before seroconversion and 1000 after seroconversion, total 1851 plasma samples). The antibodies to the 12 PCS peptides, one non-PCS Gag and one non-PCS Env peptides in these plasma samples will be analyzed using a multiplexed Bead array assay developed in the lab. The magnitude and the spectrum of the anti-PCS abs in HIV resistant women will be compared with the ones of HIV seroconverters before seroconversion. We will also compare the magnitude of plasma anti-PCS abs of seroconverters before (851 samples) and after seroconversion (1000 samples, 4 samples per seroconverter). This will help to determine whether the higher magnitude or spectrum of anti-PCS abs correlate with resistant to seroconversion. Statistical analysis will be conducted using GraphPad Prism Program.

**Anticipated results:** We anticipate that the magnitude and spectrum of anti-PCS antibodies correlate with protection against seroconversion. The broader spectrum and higher magnitude of anti-PCS antibodies will be detected in HIV-1 resistant women than in HIV seroconverters before seroconversion.

**The role of student:** The student will be trained for the multiplex bead array antibody assays, conducting plasma antibody assays and data analysis. The results of the study will be drafted as a manuscript for publication. The student will be working on the manuscript and be the first author of the manuscript.

Contact information: Ma Luo (Adjunct Professor, Department of Medical Microbiology, University of Manitoba. Email: Ma.Luo@umanitoba.ca. Telephone: 204-789-5072
Genomic instability (GI) is a dynamic process that re-organizes the genetic content of affected cells with each cell division. GI is never static, and it creates and propagates clonal diversity. The term “GI” summarizes a complex set of genetic alterations including point mutations, deletions, duplications, amplifications, insertions, translocations, rearrangements and inversions.

We measure the initiation and propagation of GI using 3D nuclear imaging and super resolution imaging of the DNA structure. This type of imaging is novel and software to quantitate the nuclear structure of DNA has been developed by our laboratory. Two projects are available for Hodgkin’s Lymphoma.

_Hodgkin’s Lymphoma (HL)._ Hodgkin’s lymphoma (HL) affects all ages, from adolescent to old age. Currently, 80-85% of the patients are cured by standard combination chemotherapies, while 15-20% relapse and/or succumb to the disease. HL has two cell types, the mono-nucleated Hodgkin’s cell (H cell) and the multi-nucleated Reed-Sternberg cell (RS cell). The RS cell is the diagnostic cell of the disease.

**Project 1.** “Characterization of DNA-poor space”. Based on previous data from our laboratory, we hypothesize that the nuclear DNA organization is key to the stability or aggressiveness of the disease. Further, we hypothesize that DNA-poor spaces detected in HL nuclei are linked to disease aggressiveness. The aim of this study is to provide evidence, based on patient samples, how DNA structure and disease stability/aggressiveness are linked. All patient samples will be studied in a blinded fashion. Clinical follow-up data are available upon project completion.

**Project 2.** “Characterization of telomeric fragments”. We recently detected telomeric fragments in DNA-poor spaces. We hypothesize that telomere maintenance is dysfunctional in HL and propose to study mechanisms of their generation. This will be done in HL cell lines. Knowledge gained from cell line work will next be translated to patient samples. All patient samples will be studied in a blinded fashion. Clinical follow-up data are available upon project completion.
Project Title: Resolving the specific immunological abnormalities in chronic lymphocytic leukemia and their relevance to patient outcomes

Background
Chronic lymphocytic leukemia (CLL) is diagnosed by the presence of malignant lymphocytes in the blood, lymph nodes, spleen and marrow. These CLL cells cause immunosuppression, leading to an increased incidence in infections and second cancers, major causes of death in this disease. While a number of alterations in immune cell numbers and function in CLL patients have been documented, the specific alterations associated with adverse patient outcomes remain poorly defined. Advances in immune-phenotyping methodology provide new opportunities to accurately assess immunological changes in CLL patient populations and test the potential association of these changes to patient outcomes.

Methods
CancerCare Manitoba is home to the CLL clinic, which follows ~1000 active patients and maintains an extensive database of patient clinical information and numerous prognostic biomarkers. The associated CLL biobank cryopreserves peripheral blood mononuclear cells and plasma from CLL and age-matched normal controls. Composition of circulating immune cells, will be assessed using established multicolor flow cytometry panels to measure frequencies of T cell, B cell, monocyte and NK cell subsets, as well as expression of activation and checkpoint receptors. Plasma will be assessed by multiplex assays to measure 35 soluble proteins relevant to immune function (cytokines, chemokines and antibodies). Patient identifier numbers assigned by the biobanking team can be used to link data to relevant information regarding disease biomarkers, prior treatments and clinical outcomes.

Anticipated Results
The overarching goal of the study is to better define the immunological abnormalities in CLL. Specifically, we aim to identify immunological signatures associated with i) Rai stage and prognostic markers, ii) CLL progression, as assessed by lymphocyte doubling, advancing Rai stage and time to first treatment (TTFT), iii) development of serious infections requiring treatment or hospitalization, iv) development of second malignancies.

Role of Student
The student will participate in ongoing data collection and analysis. This will involve learning techniques such as flow cytometry and multiplex biomarker assays, analyzing and organizing data, and querying the dataset for significant associations with clinical parameters. It is expected that the student will generate analyses and figures suitable for publication and will have potential opportunities for co-authorship.

Supervisor and contact: Dr. Aaron Marshall, Professor, Department of Immunology, aaron.marshall@umanitoba.ca; 204 789-3385

Co-supervisor: Dr. James Johnston, Professor of Internal Medicine, Senior Investigator, Research Institute in Oncology and Hematology (formerly Manitoba Institute of Cell Biology), CancerCare Manitoba
Title: Does SYNTAX score predict outcomes in Cardiogenic Shock?

Background

Cardiovascular disease is the leading cause of death worldwide. Despite advances in technology and pharmacotherapy the mortality of patients with ST-elevation Myocardial Infarction (STEMI) complicated by cardiogenic shock (CS) has not changed significantly for the last 20 years. Significant non-culprit stenosis are present in 40-70% of patients undergoing primary percutaneous coronary intervention (PPCI) [1,2]. Several studies have shown that patients with ST- elevation Myocardial Infarction (STEMI) with multivessel coronary artery disease (MVD) have worse outcomes [1, 3, 4]. The SYNTAX score is a tool that quantifies the extent of angiographic coronary artery disease. The SYNTAX score has been shown to be a good predictor of major adverse cardiovascular events in patients treated with PCI with complex disease [5-7]. In the STEMI population, both baseline SYNTAX score prior to PPCI and more recently residual syntax score (rSS) have shown increase in (MACE) [8-9]. In the setting of STEMI complicated by cardiogenic shock (CS) guideline recommendations are to proceed with complete revascularization (CR) [10]. Our group showed that CR was strongly associated with in-hospital survival in patients with CS. Recent multicenter studies have not found that CR improves outcomes in STEMI patients with CS.

Objective

This study will examine the relationship between SYNTAX score, rSS and outcomes in our population of STEMI patients with CS.

METHODS

We will retrospectively review our local STEMI database at SBGH and identify patients with CS at time of PPCI for our study population. In addition to calculating the SYNTAX score and rSS we will identify a number of baseline criteria. Our primary outcome will be a composite of in-hospital mortality, need for mechanical circulatory support, length of stay, and peak infarct size as measured by creatinine kinase and hsTnt.

Anticipated Results

We would anticipate that STEMI patients with CS who have a higher baseline SYNTAX score and higher rSS would have a higher MACE rate and worse prognosis. If the study shows that patients with a lower rSS post PPCI have an improved outcome this would support more complete revascularization in the acute setting in this population.

Role of Student

The student will be involved in the STEMI database by reviewing medical charts, data extraction, and creation of this novel data set. In addition the student will have the opportunity to learn interpretation of coronary angiograms with one-on one exposure with the Staff Interventional Cardiologist and help with calculation of SYNTAX scores and rSS. Once the first phase of the study is complete the student will be involved in preparation of the manuscript for publication.

Contact

Dr. Kunal Minhas
Assistant Professor of Medicine Interventional Cardiologist, WRHA CSP University of Manitoba
Y3541-409 Tache Ave, Winnipeg, MB, R2H 2A6

E: kminhas@sbgh.mb.ca
T: 204-237-2390
Lipid molecules as a predictive factor of treatment response to repetitive transcranial magnetic stimulation in major depressive disorder

BACKGROUND

Major depressive disorder (MDD) is a chronic illness and the leading cause of disability worldwide. Repetitive Transcranial Magnetic Stimulation (rTMS) – a non-invasive method of brain stimulation – is an effective treatment for many patients whose symptoms are otherwise treatment-resistant. However, there are currently no reliable biological characteristics or biomarkers that can help guide clinicians in choosing the right treatment for each patient. Lipidomics – the study of plasma lipids – represents a promising approach to identify new diagnostic biomarkers in MDD for the following reasons: i) brain cells are highly vulnerable to a biological phenomenon known as oxidative stress, ii) MDD is associated with high levels of oxidative stress, iii) lipid bi-products of oxidative stress can cross the blood brain barrier and be detected in blood plasma, and iv) rTMS can have a protective effect against oxidative stress. We hypothesize that response to rTMS treatment in MDD may depend on differences in enzyme metabolism between individual patients, which could be measured by differences in the oxo-lipidomic profile of plasma.

OBJECTIVE

This study seeks to identify biological markers of oxidative stress through oxo-lipidomic analysis to identify novel plasma lipid markers of a positive response to rTMS in cases of MDD. Blood samples have been taken from patients who are undergoing rTMS for MDD before and after treatment and control subjects. Lipidomic analysis will be performed to compare lipid products between patients who respond well to rTMS and those who do not.

The student will be involved in lipidomic analysis of human plasma from patients suffering from MDD and control subjects. All plasma samples are currently collected and the student will be involved in sample extraction and mass spectrometric analysis.

Contact:
Dr. Mandana Modirrousta
Neuromodulation/Neurostimulation Laboratory
M5 McEwen - St. Boniface Hospital
351 Tache Avenue, Winnipeg MB, R2H 2A6
(Phone) 204-237-2606
(Fax) 204-233-8051
(e-mail) mmodirrousta@sbgh.mb.ca
Changing Trends in Presentation and Outcome of Squamous Cell Carcinoma of the Cervical Lymph Nodes of Unknown Origin

**Background:** Cervical lymph nodes are the most common site of metastasis from squamous cell carcinoma (SCC) of the head and neck. In approximately 5% cases, no primary source of metastasis can be identified and the treatment is empirically targeted to the neck and potential primary sites. The objective of this study is to analyze the trends in management and outcome of SCC of the cervical lymph nodes of unknown origin in pre and post- PET scan era.

**Methods:** This study will involve retrospective review of electronic and paper records of a population-based cohort of about 900 patient charts from pre (about 500) and post-PET (about 400) era. Patient demographics, extent of disease at initial presentation, treatment modalities used, pathology details, cancer recurrences during the follow-up, and the final oncological status as of January 1, 2019 will be recorded and analyzed using SPSS for Windows version 23.0 (SPSS Inc.). Relapse free survival (RFS) and disease-specific survival (DSS) will be estimated by the Kaplan-Meier product limit method. Cox-proportional hazard model will be used to assess the independent influence of pre-treatment diagnosis by PET scan on the oncological outcome of patients with SCC of unknown origin.

**Anticipated Results:** We anticipate that the identification of a primary tumor prior to treatment in a greater proportion of patient in the post- PET era has not itself resulted in a better overall and disease-free survival.

**Role of the student:** The student will be involved in study design, data collection and analysis, presentations and publications.

**Contact details**

Dr. K.A. Pathak, MD, FRCSC
Professor of Surgery & Director, Surgical Fellowships, University of Manitoba
Program Director, Head & Neck Surg. Oncology Fellowship,
ON 2048, CancerCare Manitoba, 675 McDermot Avenue, Winnipeg R3E 0V9
Phone +1-204-7871340 (Office), +1-204-7872768 (Fax)
Glioblastoma Pseudoprogression: assessment, management, and decision-making.
Supervisor: Marshall Pitz MD MHS FRCP
Contact: marshall.pitz@umanitoba.ca

Background:
Glioblastoma (GBM) is the most lethal primary brain tumour in adults. Treatment consists of surgery followed by concurrent chemotherapy and radiation, followed by adjuvant chemotherapy. During this treatment, approximately 30% of patients will develop changes on MRI consistent with progression of their disease that is not associated with tumour regrowth, called pseudoprogression. Differentiating between pseudoprogression and true progression is not reliable using existing diagnostic tests, and clinicians are forced to either continue treatment (giving the patient the benefit of the doubt) and changing therapy. In either case the decision may be incorrect, either leaving a patient on a treatment that is ineffective or taking them off a treatment that would have helped them further. The rate of accuracy of clinicians in determining the best course is unclear.

Methods:
Phase 1. Using a retrospective cohort, patients with GBM will be selected using the Manitoba Cancer Registry. Treatment-related variables will be extracted in a structured format from the electronic medical record. Chart review will be required to determine: 1. which patients had evidence of progression or pseudoprogression at the appropriate time following/during treatment, 2. The decision made by the clinicians (continue treatment vs change treatment), 3. Patient outcome in each case (eventual changes consistent with progression on next imaging vs response to treatment). The rate of accuracy will be determined based on these variables. Factors consistent with either progression or pseudoprogression will be evaluated using multivariable logistic regression.

Phase 2. Using patients (de-identified) from phase 1, patients will be selected with appropriate clinical variables and images to construct a survey. Medical Oncologists, Radiation Oncologists, and Radiologists from across Canada will be invited to complete the survey. They will use the provided clinical information to decide whether patients have pseudoprogression or true progression. Additionally, they will be asked what factors they consider to be important in deciding between true progression and pseudoprogression. Results will be tabulated and rates of accuracy determined.

Anticipated Results:
We expect to characterize the diagnostic accuracy of clinicians at determining pseudoprogression versus true progression at the time of the event as well as the impacts of those decisions. Further, we expect to determine the range of these factors from across Canada.

Role of Student:
1. Development of the proposal for ethics and regulatory approval.
2. Retrospective review of clinical factors, imaging results, and decisions made by the treating team.
3. Development of the survey and capture of data.
4. Basic statistical analysis, in collaboration with a statistician.
5. Write-up, presentation, manuscript preparation and submission.
Standardization of Moderator Training for an Online Tool to Address Parental Vaccine Hesitancy

**Background:** Parental hesitancy towards childhood vaccines has become a significant public health concern across Canada and elsewhere due to decreased vaccine uptake rates and outbreaks of vaccine-preventable illness. The traditional “knowledge gap” approach to this problem has been unsuccessful as it does not always identify or address parents’ true underlying concerns and does not account for the roles that cognitive bias, emotion and risk assessment play in parents’ decision-making process. To address these issues, our research team developed an interactive online tool (Vaccine Answers), in which site moderators interact online directly with parents to address vaccination questions and concerns in an individualized manner. However, the success of this novel tool requires developing a standardized approach to train moderator(s) and ensure that best practices in communication are consistently followed to facilitate its expansion and replication in other jurisdictions.

**Methods:** A systematic literature review would be undertaken with the assistance of a medical librarian to identify studies and papers relevant to vaccine hesitancy and risk communication. Results of the literature review will contextualize findings and guide the development of a toolkit to be used for site moderator training.

**Anticipated results:** A report summarizing the current literature and findings will be developed and refined for publication with student as co-author. A multimedia toolkit including written materials, online resources and other components as guided by the systematic literature review will be produced.

**Role of the student:** The student will be involved with all aspects of the project as described above, including the systematic literature review with the librarian, writing the paper to be submitted for publication with the student as co-author, and planning/creating the moderator toolkit. A second paper specific to the toolkit development process may also be considered. It is anticipated that in year one the systematic literature review would be completed; in year two the toolkit will be developed and the paper will be prepared for publication.

Other benefits to the student include interdisciplinary networking and collaboration, development of skills to organize, interpret, and apply knowledge in vaccine hesitancy and risk communication (relevant to both research and clinical care), and knowledge translation skill development. The student may also be included in research team meetings related to the larger project, and will have opportunities to participate in clinical activities in the Family Medicine teaching clinics.

**Contact:**

Jen Potter MD CCFP  
Family Physician  
Assistant Professor, Department of Family Medicine  
Kildonan Medical Centre  
Seven Oaks General Hospital  
2300 McPhillips Street  
Winnipeg MB R2V 1M3  
Phone 204 632 3203, jpotter@sogh.mb.ca
FDA-approved Drugs for Epigenetic Studies in Neural Stem Cells

**Background:** Neural stem cells (NSC) are primary progenitors with the ability of self-renewal and differentiation into different cell types within the central nervous system of the embryonic and adult brain. Neural stem cells are widely accepted biological systems to study the basics of mammalian neurogenesis, the process in which new neurons are produced in the brain. NSC differentiation is controlled by epigenetics, with high impact in development and disease. Understanding the mechanisms of NSC differentiation is crucial, since they can be used to replace cells, which are lost or damaged in brain stroke, trauma, spinal cord injury, and other neurological disorders such as Parkinson’s or Alzheimer’s disease.

**Methods:** Using cutting edge technologies in stem cell biology, we will study the effect of specific FDA-approved drugs on the epigenetic control of gene regulation in neural stem cells. We will use a combination of stem cell cultures, RT-PCR, Western Blot, and DNA methylation studies.

**Anticipated Results:** We expect to detect increased neurogenesis during the differentiation of embryonic NSC, and to uncover the mechanism of action of these FDA-approved drugs. The outcomes are expected to be important for neurodevelopmental disorders, including autism and Rett Syndrome.

**Student's Role:** The student will be responsible for the associated experiments with this study and analyzing the data. The student will also be responsible to be up to date with regards to the literature related to this project.

**Supervisor Information:**
**Name:** Mojgan Rastegar, PhD, Associate Professor  
**Address:** Regenerative Medicine Program  
Department of Biochemistry & Medical Genetics  
University of Manitoba, BMSB # 627  
**Phone:** 204-272-3108  
**Email:** mojgan.rastegar@umanitoba.ca
Targeting Cell Signaling by FDA-Approved Drugs in Medulloblastoma Brain Tumor

**Background:** Medulloblastoma is a high-grade, malignant, and rapid growing pediatric brain tumor that resides in the cerebellum. Medulloblastoma is the most common tumor originating from the immature cells of the developing brain. In 70% of cases, medulloblastoma is developed in young children below the age of 10.

**Methods:** In a primary screen of FDA-approved drugs, we discovered selective anti-cancer effects of FDA-approved drugs. Such anti-cancer effects were only detected in human medulloblastoma cells, but not in normal human cells. In this project, we will use different types of aggressive and non-aggressive brain medulloblastoma cell lines to study the mechanisms of induced cell death for these FDA-approved drugs. The experimental procedures will include: cell culture and drug-treatments, viability tests, protein and RNA extraction from the collected samples, Western Blot and RT-PCR experiments.

**Anticipated Results:** While the effects of these drugs on specific cell signaling pathways (RAS-mTOR) are well documented in other cell types, involvement of these cell-signaling pathways for these drugs are not studied in medulloblastoma. We expect to detect a cross-talk between autophagy and apoptosis as the mechanism of cell death by these drugs in medulloblastoma. Our results will have significant therapeutic outcome for medulloblastoma as the most common brain tumor in children.

**Student's Role:** The student will be responsible for the associated experiments with this study and analyzing the data. The student will also be responsible to be up to date with regards to the literature related to this project.

**Supervisor Information:**
**Name:** Mojgan Rastegar, PhD, Associate Professor  
**Address:** Regenerative Medicine Program  
Department of Biochemistry & Medical Genetics  
University of Manitoba, BMSB # 627  
**Phone:** 204-272-3108  
**Email:** mojgan.rastegar@umanitoba.ca
**Background:** Scattered x-rays compromise image quality in fluoroscopic exams and scatter increases with patient size. The presence of barium, a contrast agent in gastrointestinal radiography, also affects the distribution of scatter, both at the detector and around the patient. Image quality and patient dose may both be impacted when imaging with barium compared with non-contrast exams.

Anti-scatter grids reduce scatter at the image receptor, but require an increase in radiation output, and thus patient dose, to maintain an adequate image signal to noise ratio. Grid usage may be necessary for larger patients to maintain diagnostic image quality. Given the greater radiosensitivity of children relative to adults, image quality improvements resulting from grid use must be balanced against the increased dose.

**Methods:** The proposed study is part of our on-going investigation into the patient size at which grid use becomes necessary to maintain adequate diagnostic quality for fluoroscopy. A phantom will be constructed containing simulated bowel coated with barium contrast agent. Additional material will be used to vary the thickness of the phantom to approximate the expected patient size range. Fluoroscopic images will be acquired with and without the use of an anti-scatter grid. The images will be evaluated by radiologists and rated using a Likert scale for bowel visibility. Aggregate results will be used to determine the patient thickness at which grid usage becomes necessary. Inter-reader and intra-reader variability will be assessed in the statistical analysis. The impact of increasing patient thickness and grid usage on patient and scatter dose will be measured.

**Anticipated results:** The anticipated outcome of the study is a recommendation on the threshold patient size/thickness for which anti-scatter grid usage would be appropriate.

**Role of the student:** The student will conduct a literature review, informing design of the phantom and identifying similar studies for comparison. Working with a trained technologist the student will acquire fluoroscopic images and dose measurements with the completed phantom. The student will carry out the statistical analysis, aided by a statistician, and write up the results in a format suitable for publication.
Title: Use of Wearable Technology in Real World Clinical Settings to Improve Patient Outcomes

Background: Advanced Chronic Kidney Disease (CKD Stages 4-5) affects more than 100,000 Canadians and leads to kidney failure (KF) in more than 10,000 individuals annually. Patients with KF require renal replacement therapy, usually dialysis, to survive. Despite close follow-up by the health teams, patients transitioning to KF experience a high rate of unplanned dialysis initiation leading to increased morbidity and mortality as well as increased use of health care resources. Strategies to improve the monitoring of CKD patients transitioning to dialysis are urgently needed.

Wearable, wireless devices are popularly used for self-monitoring of fitness, diet, and activity. Such devices, when integrated appropriately, can provide seamless home monitoring of high risk patients with chronic disease. With our technology partners at EQOL, we developed a platform called VIEWER (Virtual Ward Incorporating Electronic WEaRables), which links commercially available devices (Weigh scale, BP cuff, O2 sat monitor, activity monitor) wirelessly via a tablet interface. We will study whether VIEWER can detect subclinical deterioration, inform optimal initiation of dialysis, and improve health outcomes.

Methods: The study is structured into feasibility (Aims 1-2) and longitudinal observational (Aims 3 and 4) phases. The feasibility phase will further test the software and user interface, to establish that VIEWER works well for the intended CKD population. It will also assess that the platform remains stable over a long period of time. Finally, for the longitudinal phase we will conduct a prospective cohort study in 100 CKD patients at high risk (>80% 2-year risk) of needing dialysis, using VIEWER to collect longitudinal data on vitals (weight, BP, O2 saturation), activity, sleep, and KF symptoms. We will examine time-dependent associations between the variables captured by VIEWER and the outcome of interest (unplanned dialysis start). Furthermore, we will use accepted prediction model development approaches to develop multivariate cox regression models with which we have substantial published expertise.

Anticipated Results: At the end of the study we will have developed a fully usable VIEWER platform complete with integrated decision aids to help patients and providers decide when to start dialysis to avoid major adverse kidney events. We will then proceed in a subsequent study to conduct validation of VIEWER in a randomized controlled trial with clinical endpoints.

Role of the Student: The student will work closely with technology partners and clinician scientists at the Seven Oaks Hospital Chronic Disease Innovation Centre to carry out the proposed project that will determine feasibility, clinical outcomes, technology outcomes and patient acceptance of this device in a real world clinical context. The SOGH CDIC has a well-developed infrastructure for world class research and a proven track record of mentoring many highly successful BSc Med projects that go on to publish their work in high impact journals and present abstracts at National and International Scientific Meetings.

Contact Information:
Michelle Di Nella
204-632-3383
mdinella@sogh.mb.ca
The epidemiology and multi-disciplinary management of work-related concussion – how can we meet the needs of Manitoba’s workers?

**Background:** Brain injuries are a major cause of death and disability with a significant proportion occurring at work but the short and long-term outcomes such as returning to work, developing post-concussion syndrome (PCS), mental health outcomes, and health-related quality of life (HRQOL) remain unstudied. We will: 1) evaluate the natural history of work-related concussion and identify clinical risk factors PCS; 2) examine changes in concussion, depression and anxiety symptoms, headache disability scores, and HRQOL following acute work-related concussion and their relationship to developing PCS, post-injury psychiatric outcomes, return-to-work status, and long-term disability status; and, 3) determine outcomes when treated with multi-disciplinary rehabilitation.

**Methods:** We will conduct a prospective case-series of adult patients who sustain a concussion during a work-related activity and who are evaluated at the Pan Am Concussion Program within 2 weeks. Baseline mental health will be established. Depression, anxiety, migraine, concussion symptoms, and HRQOL surveys will be completed immediately after study enrollment and then immediately prior to each follow-up visit until the adult is medically cleared to return to full-time work. Outcomes include changes in concussion, depression and anxiety symptoms, changes in HRQOL, development of PCS, and developing post-injury mental health outcomes. We will collect time to recovery and part- and full-time return to the work force, as well as healthcare services utilized during the recovery process. Approximately 150 workers will be recruited. Mixed generalized linear modeling will assess predictors of changes in the depression, anxiety, headache disability, and HRQOL scores over time. Logistic regression will determine risk factors for developing PCS, post-injury psychiatric outcomes and long-term disability status.

**Anticipated Results:** Results will improve patient management and outcomes for those suffering from a work-related concussion. It will also determine what services and supports are needed to optimize return to work.

**Role of the Student:** They will recruit patients, conduct interview, perform medical chart reviews, enter data, analyze data and draft the manuscript. They will present their findings at local meetings.
A Tool to Predict Cesarean Delivery in Rural First Nations Populations

Alexander Singer MB BAO BCh CCFP, Kheira Jolin-Dahel MSc CCFP, Wanda Phillips-Beck RN. PhD candidate, Helga Hamilton, Julia Witt, Alan Katz, MBChB, MSc, CCFP, FCFP

**Background:** Few rural First Nations communities offer intrapartum care. Women residing in these communities must travel to a larger center for delivery. There is overwhelming evidence of adverse effect when parturient women need to travel for care. A clinical decision tool that helps predict the likelihood of a successful vaginal delivery would be of great benefits to the both health care providers and patients.

**Objectives:** Primarily, to determine the applicability of a previously published tool to predict cesarean delivery in low risk pregnant women from a rural First Nations community. Secondly, to create an application for mobile phones whereby health care providers can input the variables that are specific to their patient and the risk of cesarean delivery would be automatically calculated.

**Methods:** We will conduct a retrospective chart review of all low risk women from Cross-Lake First Nation Community. Based on a previously published model, a series of antepartum and intrapartum maternal factors will be applied using a univariate logistic regression models, to calculate the risk of an unplanned caesarean birth.

**Anticipated Results**
We will determine the rate of unplanned cesarean birth versus estimated rate of unplanned cesarean birth based on the scoring systems applied. Secondary outcomes will include immediate maternal and neonatal complications. This will serve to support implementation of local low risk intrapartum services in Cross-Lake and across other rural and First Nation communities.

**Role of the student**
The student will then be responsible for conducting the chart review and descriptive statistical analysis in consultation with the research team. Once results are available the student will prepare the first draft of the manuscript and participate editing future drafts.
Split-dose Bowel Preparation for morning Colonoscopy: A Pragmatic Randomized Controlled Trial

**Background:** Previous studies suggest a significant proportion of colorectal cancers and precursors are missed on colonoscopy. Split-dose Bowel Preparation (SDBP) for colonoscopy has been shown to provide better bowel cleansing than day before bowel preparation (DBP) and is a strongly recommended for all patients in North American and European guidelines and results in better detection of lesions. However, health care providers and patients continue to be reluctant to use SDBP for the morning colonoscopy patients because of perceived inconvenience for night time sleep and early morning awakenings. Health care providers are also concerned about the extra workload that routine use of SDBP for morning patients could generate in terms of patients phone calls for concerns, appointment rebooking, last minute appointment cancellations and/or no shows. There are concerns that subjects included in clinical trials were those willing to participate in trials and the results may not be fully generalizable to usual clinical practice.

**Methods:** We are planning a pragmatic RCT comparing current practice to routine use of SDBP among adult patients undergoing colonoscopy in the morning endoscopy slates.

**Patients:** All adult patients undergoing outpatient colonoscopy in morning at one hospital site

**Intervention:** Instructions to use SDBP, supported by a website providing educational information on SDBP and other aspects of colonoscopy

**Comparison:** Routine care

**Outcomes:**

**Primary outcomes:**

1. What proportion actually took SDBP?
2. Composite outcome; Proportion with cancellations in the day before colonoscopy and no shows

**Secondary outcomes:** Bowel cleansing scores, specific lesion rates, Patient convenience such as subject willingness to repeat the preparation

**Anticipated results:** Would provide data on whether recruited volunteers randomized control trials data can be generalized to routine care.

**Student role:** Patients interview, data recording

**Contact Information:** Harminder.singh@umanitoba.ca
Title: Frailty affects treatment decisions and outcomes for patients with chronic kidney disease

**Background:** Chronic kidney disease (CKD) is a major public health problem with increasing incidence and prevalence in North America and worldwide. CKD disproportionately affects the elderly, and leads to higher risks of kidney failure, cardiovascular events and all-cause mortality. In this population, CKD is also associated with additional comorbid conditions, and an increased prevalence of frailty and disability.

Frailty is a multidimensional syndrome characterized by loss of lean body mass (sarcopenia), weakness, and decreased endurance, leading to reduced activity and a poor response to stressors. Several prospective studies in the general population have shown that measures of frailty are strongly associated with death and hospitalization in older individuals, and moreover that this association is independent of other clinical risk factors and comorbid conditions.

**Methods:** We are presently conducting a prospective cohort study examining frailty in individuals with advanced CKD. Our study will enroll 600 patients with CKD Stages 4-5, and perform tests of physical function and cognition. We will then associate frailty and its components (physical function, cognition, depression) with treatment preferences and adverse outcomes in the CKD population. The cross sectional component of this study was completed in July 2016, and the longitudinal analysis will begin in June 2018.

**Anticipated Results:** We believe that frailty is highly prevalent in patients with CKD, and is associated with treatment decisions and outcomes.

**Role of the Student:** The student will join our multidisciplinary research team at the Chronic Disease Innovation Centre (CDIC) at Seven Oaks Hospital, and participate in every aspect of this prospective study. Responsibilities will include patient enrollment and consent, frailty evaluation, data abstraction and management, and participation in statistical analysis and manuscript preparation. Our research group has a co-supervision model; this study will be primarily supervised by Dr. Tangri with additional CDIC investigators acting as co-supervisors. The CDIC has a well-developed infrastructure for world class research and a proven track record of mentoring many highly successful BSc Med projects that go on to publish their work in high impact journals and present abstracts at National and International meetings.

**Contact Information:**
Michelle Di Nella
204-632-3383
mdinella@sogh.mb.ca
Background: Vast improvements have been made to bearing materials used in joint replacement – particularly in total hip replacement. Since the 1960’s, polyethylene (PE) has been used in hip replacements with ever increasing level of sophistication resulting in drastic improvements in material durability. Quality of manufacture of the base resins (GUR 1020 / 1050), optimized sterilization methods, re-melting/annealing following sterilization, PE chain cross-linking, and antioxidant infusion are some of the main improvements made to this material over the past 50 years. There is a lack of published literature regarding the susceptibility of different PEs to oxygen and how this affects their wear resistance, partly because manufacturers do not wish to share such information. There is a need for a robust comparison between modern PE types following exposure to mild and more severe oxidative environments to truly establish their long-term clinical durability.

Purpose: To establish oxidative index on variants of ultra-high molecular weight polyethylene (UHMWPE) for total hip replacements following accelerated aging.

Year 1)

Methods: Acetabular polyethylene liners of conventional, cross-linked, and antioxidant stabilized varieties will be obtained and subject to accelerated aging following the ASTM F2003-12 testing standard. The liners will be sectioned into 5 portions, with each portion undergoing different durations of accelerated aging as per Table 1. The aging method involves an 97%+ oxygen environment under a constant pressure of 73 psi and heated to 70°C. Prior to and following accelerated aging, the insert sections will be stored at -86°C to prevent further aging. All aging processes will be completed prior to the start of the BSc Med term.

The oxidative index of each insert section will be evaluated using Fourier-Transform infrared spectroscopy (FTIR) following ASTM F2102-13 guide. The level of oxidation index and penetration of the oxidative line (thin white band) into the polyethylene surface will be compared within material groupings to determine the effect of aging duration. Similarly the index and penetration will be compared between material types for each time point to determine each materials resistance to oxidation.

Table 1: Sections of polyethylene inserts to be extracted from the aging vessel at specified time points.

<table>
<thead>
<tr>
<th>Poly Insert Material</th>
<th>0 Weeks (Control)</th>
<th>2 Weeks</th>
<th>4 Weeks</th>
<th>6 Weeks</th>
<th>10 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
</tr>
<tr>
<td>XLPE</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
</tr>
<tr>
<td>Vit-E XLPE</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
<td>1/5</td>
</tr>
</tbody>
</table>
The student will:

Perform a literature review of polyethylene oxidation in joint replacement, polyethylene treatments to improve wear/oxidative resistance, and review the relevant ASTM testing standards.

Learn the theory and application of FTIR, perform FTIR measurements on all samples, collect and interpret the data.

Develop an initial write-up of the project including and introduction and background to the research, methodology used, results obtained, and discussion on the relevance to clinical practice.

**Year 2:**

In tandem with aging of the 1/5 sections of liners, 4 whole inserts of each material type will undergo 10 weeks of accelerated aging. The inserts will then be tested in a hip simulator for 5 million cycles as per ISO 14241-3 to establish the steady-state wear of each material type. Samples will be stored in a -86°C freezer prior to testing to prevent further oxidation.

Wear testing will occur prior to the start of the summer, 2019. The student will analyze the specimens and assess the implant wear based on deformation and changes in material weight. They will then perform the statistical analyses with the supervision of the research staff.

The student will then finalize the write-up including the wear data and prepare the paper for publication.
**Community member perspectives on models of care in remote isolated northern Manitoba First Nation communities**

- Dr. Ian Whetter and Dr. Sara Goulet (P.I), Dr. Sharon Bruce (collaborator)

**Purpose:** The purpose of the study is to explore the perspectives of First Nations community members’ around models of primary care, specifically physician patterns of care.

**Background:** Benefits of continuity of care for patients, including improvement in health care outcomes and satisfaction, are well documented in the literature for the general population. While we can infer that continuity of care is beneficial for all population groups, many difficulties exist in providing consistent physician services to remote communities. Little is known about the experience of primary care in remote, isolated northern Indigenous communities at this time. Colonization, culture and racist systemic practices all may impact the patient experience, outcomes and satisfaction.

**Objectives:**
1) Explore the experience of primary care for community members in remote isolated First Nations communities
2) Determine which physician care models would be preferred to meet the needs of remote isolated First Nations communities in northern MB

**Methods:** A qualitative study with data gathered through the form of interviews with at least 10 community members in a remote isolated First Nations community in Manitoba. The interviews will be coded in Invivo and patterns will be pulled to find trends in opinions, values and ideas.

By December 2017, the two PI’s will have finalized a research agreement with one of the communities in which they provide primary care services.

**Anticipated Results:** We anticipate that patients will prefer to have a multi-year longitudinal relationship with their physician, even if the trade-off is intermittent care (i.e. 1-2 weeks of service per month) versus having a physician in the community more frequently, but for a shorter period of time.

**Role of the Student:** The student will work in partnership with the community in the design and conduction of the research project. Specifically, the student will refine and update our literature review to assess the current knowledge regarding physician care models for remote communities. The student will work with the PI and community informants to design an interview tool for conducting the qualitative research. In collaboration with the PIs, they will arrange interviews with community members and travel to the community to conduct the interviews. The student will analyze the coded interviews and make conclusions and recommendations regarding the experiences of community members and their views on optimal care models. Finally, the student will write a paper outlining their research, its findings and a strategy for sharing the knowledge with community and policy makers.

Contact: Dr. Ian Whetter, email: ian.whetter@umanitoba.ca, phone: 204-795-2735
**Background:** Uncontrolled inflammation is a causative or perpetuating factor in many human disorders including obesity and atherosclerosis. Omega-3 fatty acids, including marine-derived docosahexaenoic acid (DHA) and plant-derived α-linolenic acid (ALA), can modulate inflammatory pathways and ameliorate hypertension in some individuals, but the mechanisms by which these functions are carried out are not clear. Both omega-3 and omega-6 fatty acids can be converted to bioactive metabolites known as oxylipins. Some DHA oxylipins possess direct anti-inflammatory properties, however, little functional information is available for ALA oxylipins. We hypothesize that supplementation with ALA, which is more abundant in our diet than DHA, will robustly reduce inflammation and improve cardiovascular function equivalent to DHA via the formation of anti-inflammatory oxylipins.

**Methods:** Twenty-four obese females will be recruited for a crossover design clinical study where they will be provided 4g/day of either ALA or DHA for four weeks. At Day 0, 3 and 28, plasma samples for quantifying oxylipin and cytokine levels will be obtained and pulsewave velocity measurements acquired to provide an assessment of large artery stiffness. Correlation analysis will be performed to identify associations between particular lipid metabolites and improvements in inflammation and arterial stiffness.

**Anticipated results:** We expect that ALA and DHA will target different inflammatory markers and that changes in certain oxylipins induced by supplementation will correlate with changes in cytokine production and arterial stiffness. These analyses will reveal candidate lipids for validation either as direct bioactive mediators or as biomarkers of blood vessel function.

**Role of the student:** The student will be involved in all aspects of the clinical trial, including patient recruitment, clinical measurements (including pulsewave velocity), sample processing, and statistical analysis.

**Contact:** Peter Zahradka, Dept Physiology & Pathophysiology (peters@sbrc.ca, 204-235-3507)
PROJECT TITLE: Evolution and Characterization of Multi-Drug Resistant (MDR) Streptococcus pneumoniae Causing Invasive Infections in Canada: SAVE 2011-2018

SUPERVISOR’S: Dr. George G. Zhanel* (ggzhanel@pcs.mb.ca; 204 787-4902), Dr. Heather Adam

Department of Medical Microbiology/Infectious Diseases, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada

Total Character Count 1956

Introduction

Streptococcus pneumoniae (pneumococcus) is a globally distributed, respiratory and invasive pathogen. S. pneumoniae frequently display a multidrug-resistant (MDR, resistant to ≥3 classes of antimicrobials) phenotype and we hypothesize that both antimicrobial usage and vaccine (PCV13) usage is influencing the dissemination of successful MDR clones.

Objectives

i) To assess the antimicrobial resistance patterns in MDR S. pneumoniae in Canada 2011-2018.

ii) To assess patient demographics associated with infections caused by MDR S. pneumoniae.

iii) To assess genotypic/phenotypic relatedness of MDR S. pneumoniae.

iv) To demonstrate the influence of PCV13, Prevnar ® on the epidemiology of MDR S. pneumoniae.

v) To study the virulence of MDR S. pneumoniae.

Methods

Bacterial Isolates will be obtained from the SAVE study, a national, Health Canada endorsed surveillance study assessing the prevalence of invasive pneumococcal disease in patients affiliated with medical centers from across Canada. We obtain ~1200 Streptococcus pneumoniae per year. S. pneumoniae isolates that are MDR (concomitantly resistant to 3 or more different antimicrobial classes will be studied). It is estimated that ~2-3% of isolates each year are MDR thus the entire cohort (2011-2018) should represent ~200-250 MDR organisms.

Antimicrobial Susceptibility Testing will be performed using Clinical and Laboratory Standards Institute (CLSI) guidelines.

Serotyping will occur using the Quellung reaction method using sera from the Statens Serum Institut (Copenhagen, Denmark).

Genetic Relatedness will be assessed using Multi-locus sequence typing (MLST).

Assessment of Virulence will be assessed by detecting the presence of PI-1 and PI-2 adhesion pilus-encoding islets.

Anticipated Results

MDR S. pneumoniae will be found in all regions/patient demographics in Canada, will be genetically related and possess virulence properties. PCV13 will select out non-vaccine (PCV13) serotypes.

Role of Student

The student will be involved in all aspects of the study from planning, performing all experiments, analyzing data, presenting the data and writing the report. Also the student will submit an abstract to a national/international medical microbiology/infectious diseases meeting.
Investigation of Diabetes mellitus type 2 effect on neuronal cell in an in vitro model of CNS diabetic encephalopathy

**Background:**
Increasing incidence of Diabetes is an alarming global health resulting in debilitating conditions for patients and massive cost for the health care system. Diabetic neuropathy (DN) is a systemic disease and affects multiple systems. DN is well studied in peripheral nervous system, however owing to the fact that the brain is an insulin-independent organ, diabetes effects on central nervous system neurons remains largely unknown. However in recent years it has been shown that chronic diabetes is associated with loss of memory and cognitive function. This condition is known as Diabetic Encephalopathy (DEN). The mechanism of cell death and effective pharmacological treatment is currently unknown.

Our lab is interested in thioredoxin (Trx) system, a major regulator of cell death and survival under oxidative stress conditions. Oxidation of proteins/lipids/nucleic acids is a major event in initiation of cell death. Trx is one of the two major systems that provides reducing protons for rescuing these oxidized macromolecules. Protective role of Trx has been shown in many conditions including in diabetes. In diabetes, a natural inhibitor of Trx, known as Thioredoxin Inhibiting Protein (Txnip) is upregulated in insulin-producing cells in Pancreas to negatively regulate insulin production. Txnip also binds to Trx, and prevent its reducing capacity which results in exacerbation of oxidative stress and results in β-cell death and further insulin deficiency. Inhibition of Txnip using Metformin has shown to be effective in reversing the β-cell death in models of diabetes, but remains to be investigated for DEN.

**Methods:** We have designed a proof of principle project to investigate the effect of Metformin on neurons in a culture model of DEN. Neurons will be cultured in normal and high levels of glucose. Metformin will be added to the cultures and cell viability will be assessed using biochemical and molecular biology approaches. Additionally, cellular models lacking Txnip gene will be used to further investigate the effect of Metformin on neurons. Western blotting will be used to determine any changes in expression of markers of cell death and cell survival.

**Statistical Analysis:** Data will be analyzed using Prism GraphPad, and appropriate student t-Test and ANOVA will be used.

**Expected Results:** We expect that Metformin will modulate the level of Txnip and will improve cell survival.

**Student Role:** The student will be trained properly to perform neural cell culture, and biochemical analysis of any changes in cells' health.
Laparotomy or peritoneal drainage for the management of surgical necrotizing enterocolitis and spontaneous intestinal perforation

Background

Necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) are devastating disorders of premature infants that frequently require surgical intervention. Despite recent prospective multicentre randomized trials and systematic reviews of the literature, the best surgical strategy for these patients remains unknown.

Methods

We will perform a retrospective cohort study of preterm infants with surgical NEC or SIP. Cohorts will be defined by the intended surgical management strategy, laparotomy or peritoneal drainage. Medical records at Health Sciences Centre and St. Boniface Hospital will generate a list of all children diagnosed with NEC or SIP from 2001 to 2016. Only patients with surgical NEC or SIP as defined by the Bell criteria will be reviewed. Data will be abstracted from charts into a REDCap database.

The primary outcome to be measured will be survival at 1 month, 3 months and 6 months of age. Secondary outcomes to be measured will be systemic, ventilator and nutritional support at the same time points. Time to full enteral feeds, total length of hospital stay, recurrent NEC, abdominal abscess, intestinal fistulas, intestinal strictures, short bowel syndrome and stoma complications will also be compared.

Analysis between the two cohorts will be performed with Chi-square testing. Subgroup analysis will compare the same outcomes between patients with birth weights less than or greater than 1000 grams.

Anticipated results

We expect 150 patients will meet the inclusion criteria. We expect that the conservative nature of our surgical practice pattern will demonstrate a preference for drainage over laparotomy but the primary outcome, survival, may be better for patients initially treated with laparotomy.

Role of the student

The student will assist with preparation of the REB application and the HSC and St. Boniface facility impact applications. The student will aid in the design of the REDCap data collection instruments, will perform the chart reviews, and assist with the data analysis.

Contact

Dr. Suyin A. Lum Min

slumming@exchange.hsc.mb.ca r. Suyin A. Lum Min